tion in the rate of angiographic restenosis at six months with the stenting procedure. This reduction was associated with a reduction in the need for repeat revascularization due to ischemia-associated restenosis.

Our findings contrast with those of previous investigations that examined the efficacy of pharmacologic agents in preventing restenosis.[17-24] Of the newer interventional procedures, only directional atherectomy has been subjected to careful prospective, randomized studies to assess its efficacy in reducing restenosis, as compared with the efficacy of angioplasty.[7,8] Those studies showed either no benefit of atherectomy or a minimal reduction in restenosis with more frequent major complications.

Like the Coronary Angioplasty versus Excisional Atherectomy Trial (CAVEAT),[7] our study shows that the most important determinant of the luminal diameter at six months was the luminal diameter achieved immediately after the procedure. It seems plausible that the reduction in restenosis in our stent group was due to the significantly larger luminal diameter obtained immediately after placement of the stent, as compared with the luminal diameter immediately after angioplasty. The residual stenosis in the stent group (19 percent) was roughly half that in the angioplasty group (35 percent) and 10 percentage points less than the residual stenosis in patients undergoing directional atherectomy.[7] Although the larger immediate gain in luminal diameter was offset by a larger subsequent loss, the net gain remained larger in the patients in the stent group (Fig. 1). Multivariate analysis showed that the luminal diameter immediately after the procedure was the most powerful predictor of the luminal diameter at follow-up, regardless of whether stenting or balloon angioplasty achieved this result. Therefore, it was not the specific technique used, but rather its efficacy in achieving a larger luminal diameter that was the determining factor, an idea that has been suggested previously.[25] In addition, stenting resulted in a larger diameter with less risk of intimal disruption and elastic recoil, thereby acting as an effective intravascular scaffold. The ability of the stent to serve as a scaffold was further demonstrated in the 14 patients in the angioplasty group (6.9 percent) who were switched to stent placement for treatment of imminent or actual closure after balloon angioplasty had failed. At the inception of this trial, stent placement as a bailout measure, which at the time was not available as a routine procedure, was considered equivalent to emergency coronary-artery bypass surgery. Thirteen of the 14 patients who underwent stent placement as a bailout measure had balloon-induced dissections or luminal compromise associated with chest pain or electrocardiographic changes, suggesting that these patients would have had serious clinical events if stent placement had not been available. Therefore, the availability of stent placement probably decreased the rate of clinical events in the angioplasty group. This study thus represents a comparison of two treatment strategies: elective stent placement and elective balloon angioplasty with stent placement available as a bailout measure.

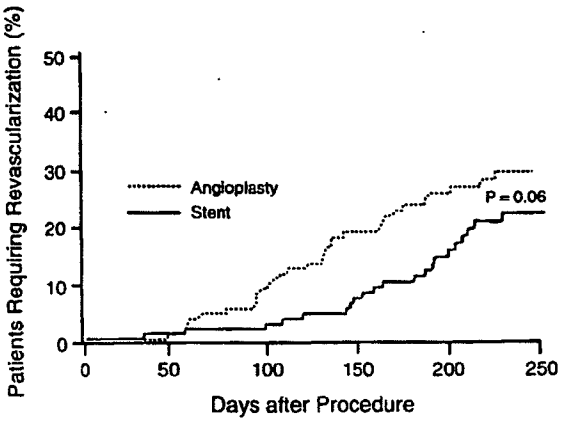

Figure 2. Kaplan–Meier Curves for Revascularization of the Target Lesion.

Fewer patients in the stent group than in the angioplasty group required revascularization of the target lesion because of ischemia.

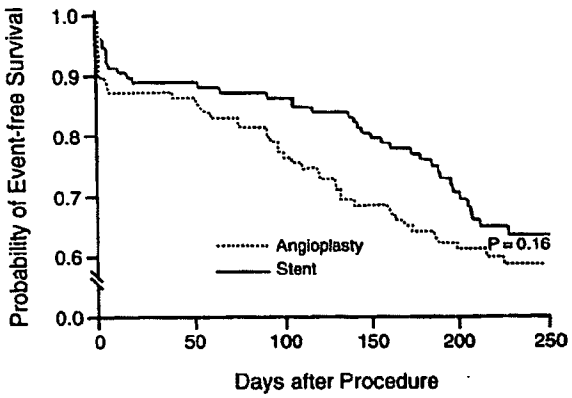

Figure 3. Kaplan–Meier Survival Curves for Major Cardiac Events (Death, Myocardial Infarction, Coronary-Artery Bypass Surgery, and Repeated Angioplasty).

Several limitations of stent placement need to be emphasized. Stent thrombosis occurred in 3.4 percent of the patients who underwent stent placement as an elective procedure and in 21.4 percent of those in whom stent placement was used as a bailout technique. These thrombotic events occurred 2 to 14 days after placement of the stent, with six instances of thrombosis after discharge, and invariably resulted in major clinical complications. Furthermore, the intense anticoagulation and antiplatelet regimen associated with stent placement resulted in nearly twice the number of hemorrhagic and peripheral vascular complications associated with angioplasty, as well as a prolonged hospital stay.

Although the frequency with which follow-up angiography was performed was relatively high in both

groups, there was a higher rate of angiographic follow-up in the stent group (92 percent vs. 83 percent, $P = 0.008$). This difference, which may bias the rate of restenosis in favor of stent placement, is a limitation of the study.

In conclusion, elective stent placement, as compared with angioplasty, has a higher clinical success rate and reduces the incidence of restenosis and the need for subsequent revascularization of the treated lesion. The reduction in restenosis is not associated with an increase in major cardiac events, despite the limitations imposed by stent thrombosis and hemorrhagic complications. The use of antithrombotic stent coatings, improved techniques to optimize expansion of the stent during implantation, and compression and closure devices at the site of arteriotomy may address these limitations. If they are effectively overcome, implantation of the Palmaz–Schatz stent may become the preferred treatment in selected patients with new lesions in large coronary arteries.

Appendix

The following institutions and investigators participated in the STRESS trial: Arizona Heart Institute, Phoenix (E. Davis, W. Catran, and K. Waters); Beth Israel Hospital, Boston (D.J. Diver, J. Carrozza, and C. Senerchia); Centro Cuore Columbus, Milan, Italy (Y. Almagor and M. Bernati); Cleveland Clinic Foundation, Cleveland (P. Whitlow); Florida Heart Hospital, Orlando (C. Curry, C.B. Saenz, W.H. Willis, Jr., R.J. Ivanhoe, and N. Granger); Hospital of the University of Pennsylvania, Philadelphia (H. Herman, D. Kolansky, W. Laskey, and D. DiAngelo); Johns Hopkins Hospital, Baltimore (V. Coombs); Lenox Hill Hospital, New York (E.M. Kreps, J. Strain, N. Cohen, J. Higgins, and C. Undemir); Scripps Clinic and Research Foundation, San Diego, Calif. (N. Morris and M. Dowling); St. Luke's Hospital, Houston (M. Harlan and B. Lambert); Thomas Jefferson University Hospital, Philadelphia (A. Zalewski, P. Walinsky, and D. Porter); Toronto General Hospital, Toronto (L. Lazzam, C. Lazzam, and P. Slaughter); University of Texas at San Antonio, San Antonio (J.P. Hennecken, S. Kiesz, and A. Briscoe); Vancouver General Hospital, Vancouver, B.C. (C.E. Buller and A. McCarthy); Victoria General Hospital, Halifax, N.S. (B. O'Neil, C.J. Foster, C.M. Peck, K.A. Foshay, and N.L. Fitzgerald); Victoria Hospital, London, Ont. (N. Murray-Parson and L. Marziali); Washington Cardiology Center, Washington, D.C. (K. Donovan); Yale University, New Haven, Conn. (H.S. Cabin and R.E. Rosen); *Data Coordinating Center:* Department of Epidemiology, University of Pittsburgh, Pittsburgh (K. Detre, V. Niedermeyer, L. Kennard, and L. Vetri); *Core Angiographic Laboratory:* Thomas Jefferson University Hospital, Philadelphia (R. Rake, S. Gebhardt, D.L. Fischman, M.P. Savage, and S. Goldberg); *Steering Committee:* D.S. Baim, S. Goldberg, M.B. Leon, I. Penn, and R.A. Schatz.

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The American Journal of Cardiology

DECEMBER 1, 1995

EXCERPTA MEDICA, INC., A REED ELSEVIER MEDICAL PUBLISHING COMPANY

Combination of *Lovastatin, Enalapril,* and *Colchicine* Does Not Prevent Restenosis After Percutaneous Transluminal Coronary Angioplasty

Mark Freed, MD, Robert D. Safian, MD, William W. O'Neill, MD, Maureen Safian, RN, Denise Jones, RN, and Cindy L. Grines, MD

Trials using single-agent pharmacotherapy have failed to demonstrate a significant reduction in restenosis after percutaneous transluminal coronary angioplasty (PTCA), possibly because of the lack of drug activity at the time of PTCA-induced injury and/or the likelihood that >1 mechanism is operative. A multidrug strategy begun before PTCA would address both of these issues. We therefore conducted an open-label pilot trial using lovastatin, enalapril, and colchicine to inhibit neointimal hyperplasia and extracellular matrix formation.

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Fifty patients were enrolled in the Beaumont Interventional Group–Mevacor, ACE Inhibitor, Colchicine study. Inclusion criteria consisted of age 18 to 80 years, the presence of either stable, unstable, or postinfarct angina, and angiographic evidence of ≥1 coronary lesion with ≥70% diameter stenosis. Patients were excluded from enrollment for the following reasons: known hypersensitivity to any of the study drugs; concurrent use of immunosuppressive agents, potassium-sparing diuretics, gemfibrozil, niacin, or fish oils; active liver disease; unexplained elevation of serum transaminases; angioedema; depression; a history of psychiatric illness; myocardial infarction within 3 days; and creatinine ≥1.8 mg/dl, hyperkalemia, or neutropenia.

Before the initiation of drug therapy, patients underwent a physical examination, electrocardiography, chest x-ray, and laboratory analysis consisting of a complete blood and platelet count, prothrombin and partial thromboplastin times, electrolytes, creatine phosphokinase, blood urea nitrogen, creatinine, total cholesterol, and lipoprotein and triglyceride levels. Drug administration, started 5 to 15 days before PTCA and continued until the time of follow-up angiography, included lovastatin (20 mg orally twice daily), enalapril (2.5 to 10 mg orally twice daily to maintain systolic blood pressure ≥100 mm Hg), and colchicine (0.6 mg orally twice daily). Aspirin (325 mg/day orally) was administered at least 1 day before PTCA and continued throughout the study period. The use of other medications was left to the discretion of the primary physician. PTCA was performed using conventional materials and techniques.

Lesion morphology was coded according to the modified American College of Cardiology/American Heart Association classification system.[1] Digital electronic calipers were used to determine the minimal lumen and reference artery diameters, as previously described.[2] Percent diameter stenosis was calculated at baseline, immediately after PTCA, and at the time of repeat angiography.

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Anginal status was assessed 2, 8, and 16 weeks after PTCA, and cholesterol and liver function tests were measured 8 and 16 weeks after PTCA. Coronary angiography was repeated no sooner than 4 months after PTCA, except for recurrent symptoms or a positive stress test.

Procedural success was defined as a residual diameter stenosis <50% without death, myocardial infarction, or the need for emergency bypass surgery. Restenosis was defined as follow-up diameter stenosis of >50%. Late loss in lumen diameter, the primary end point of the study, was defined as the difference between the lumen diameter immediately after PTCA and at the time of follow-up angiography, as previously described.[3]

Assuming that the typical angioplasty population has a mean late loss in lumen diameter of 0.4 ± 0.5 mm,[4] we determined that 45 lesions would be necessary to detect a 50% reduction in late loss with a power of 0.90. Statistical significance was determined from 95% confidence intervals.

The study group consisted of 69 narrowings in 50 patients (mean age 61 ± 10 years and mean ejection fraction 56 ± 9%). Baseline clinical characteristics and angiographic findings are listed in Tables I and II.

TABLE I Baseline Clinical Characteristics in 50 Patients

Characteristics	Number of patients (%)
Men	37 (74)
Systemic hypertension	25 (50)
Diabetes mellitus	9 (18)
Cigarette smoking	13 (26)
Cholesterol >200 mg/dl	33 (66)
Ejection fraction <0.40	5 (10)
Class IV angina	14 (28)
Previous:	
Q-wave myocardial infarction	15 (30)
Balloon angioplasty	16 (32)
Coronary bypass grafting	9 (18)

TABLE II Baseline Angiographic Characteristics of 69 Lesions

Lesion Characteristics	Number of lesions (%)
Type	
A	13 (19)
B1	12 (17)
B2	28 (41)
C	16 (23)
Long (>10 mm)	22 (32)
Ostial/origin	8 (12)
Eccentric	31 (45)
Angle >45°	6 (9)
Bifurcation	16 (23)
Proximal tortuosity	17 (25)
Ulceration	8 (12)
Total occlusion	6 (9)
Thrombus	2 (3)

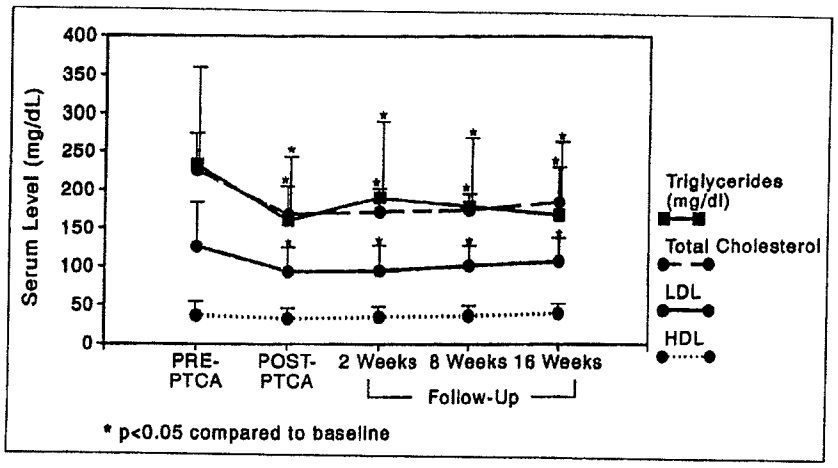

FIGURE 1. Total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels at baseline (before [PRE] drug therapy or percutaneous transluminal coronary angioplasty [PTCA]), immediately after [POST] PTCA, and during follow-up.

Plasma concentrations of lipids, lipoproteins, and triglycerides are shown in Figure 1. Two thirds of patients had baseline cholesterol levels >200 mg/dl. At the time of hospital discharge, there were reductions in total cholesterol, low-density lipoprotein cholesterol, and triglycerides of 23%, 21%, and 26%, respectively, which persisted throughout the study period. Drug therapy had no impact on high-density lipoprotein cholesterol levels.

Adverse effects requiring discontinuation of ≥1 drugs occurred in 18% of patients. The most common adverse effect was colchicine-induced diarrhea (18%), often resulting in dosage reduction or drug discontinuation. Other adverse effects were uncommon and included elevated liver transaminases >3 times control, fatigue, new cough, and nausea (1 patient each), and hair loss (2 patients).

Procedural success, defined as a residual diameter stenosis <50% without death, myocardial infarction, or the need for emergency bypass surgery, occurred in 49 of 50 patients (98%). During follow-up (5 ± 1 months), 36% of patients experienced class III or IV angina and 48% of patients required a repeat revascularization of the target lesion. There were no deaths or myocardial infarctions, and no difference in clinical outcome between patients who did (n = 40) and did not (n = 10) continue to take 3-drug therapy.

PTCA resulted in a significant increase in lumen diameter and decrease in diameter stenosis (Figure 2). The acute gain in lumen diameter was 1.1 ± 0.6 mm. Follow-up angiography in 43 of 49 patients (88%) at 5 ± 1 months after PTCA revealed a late lumen diameter of 1.4 ± 0.8 mm, diameter stenosis of 51 ± 24%, and late loss in lumen diameter of 0.5 ± 0.8 mm (95% confidence intervals 0.31 to 0.69 mm). The cumulative frequency distribution of percent diameter stenosis indicated that 53% of lesions had a >50% stenosis during follow-up angiography (Figure 3). There were no differences in late loss or percent diameter stenosis between patients receiving 3 drugs and those requiring discontinuation of ≥1 drugs because of adverse effects.

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Despite the combination of lovastatin, enalapril, and colchicine starting 1 week before PTCA and continued until the time of follow-up angiography, neither the amount of intimal thickening (late lumen loss of 0.5 ± 0.8 mm: 95% confidence interval 0.31 to 0.69 mm), the

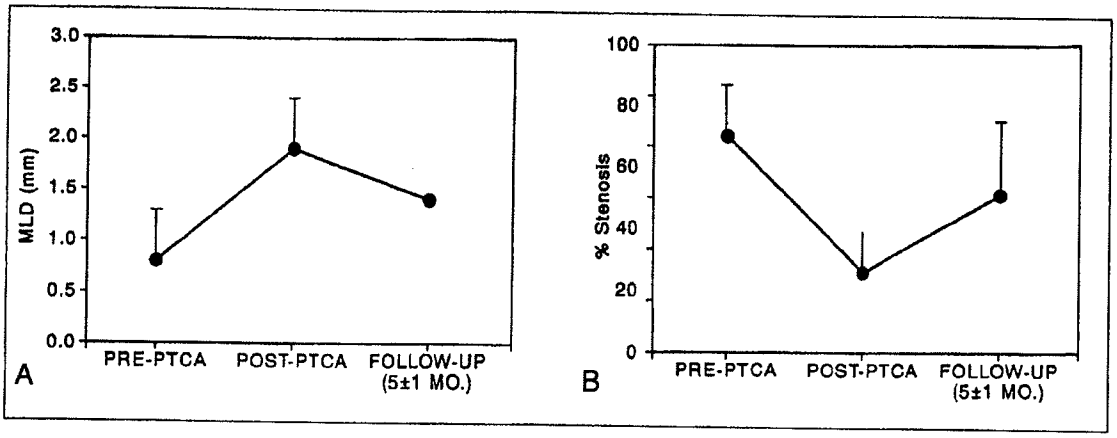

FIGURE 2. *A*, minimal lumen diameter (MLD) before (PRE) and immediately after (POST) percutaneous transluminal coronary angioplasty (PTCA), and at the time of follow-up angiography. *B*, percent diameter stenosis before and immediately after PTCA, and at the time of follow-up angiography.

development of class III or IV angina (36%), nor the need for repeat revascularization (48%) suggested a beneficial effect for this aggressive pharmacologic approach.

Single-agent pharmacotherapy has failed to reduce restenosis, possibly because of the lack of drug activity at the time of PTCA or the likelihood that >1 mechanism may be operative. A multidrug strategy instituted before PTCA would address both of these issues. We hypothesized that if restenosis was a specialized form of wound healing, as conceptualized by Forrester et al,[5] then inhibiting the inflammatory phase (influx and activation of platelets and monocytes resulting in the secretion of growth factors), granulation phase (migration and proliferation of medial smooth muscle cells), and extracellular matrix phase (elaboration of proteoglycans and collagen by fibroblasts and smooth muscle cells) of wound healing would inhibit restenosis. Lovastatin, enalapril, and colchicine were chosen based on the results of cell culture and animal studies.[6–16]

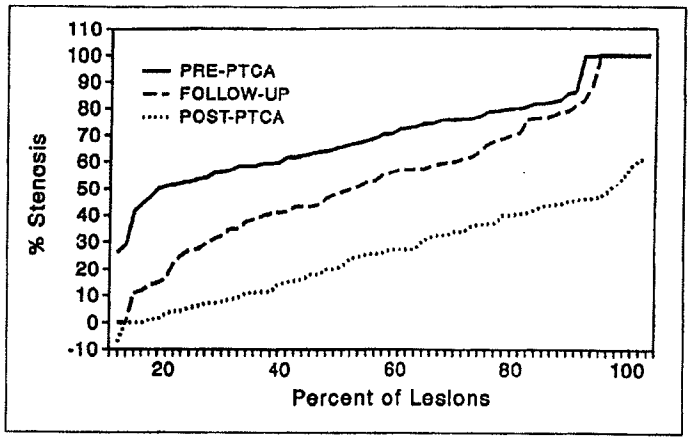

FIGURE 3. Cumulative frequency curves of percent diameter stenosis before (PRE) and immediately after (POST) percutaneous transluminal coronary angioplasty (PTCA), and at the time of follow-up angiography.

Despite an attempt to block each phase of the wound healing process, combination drug therapy failed to inhibit the late loss in lumen diameter after PTCA. Several explanations may account for this result. First, elevated lipid and angiotensin II levels may not be important in the pathogenesis of restenosis in human coronary arteries. Although lovastatin,[15] angiotensin-converting enzyme inhibitors,[10] and colchicine have been shown to reduce restenosis in preclinical models, their apparent failure in this and other clinical studies[4,17,18] underscores the limited ability of animal studies to predict the effect of drug therapy on restenosis in human coronary arteries.[19] Second, the drug dosages used in the current study may have been too low. Animal studies demonstrating a beneficial effect for lovastatin,[15] colchicine, and the angiotensin-converting enzyme inhibitor cilazapril[10] used dosages that were 5-, 12-, and 70-fold higher than those normally prescribed to humans. If higher concentrations of the drugs had been delivered to the PTCA site by drug-impregnated stents or porous balloons, beneficial effects might have been seen. Third, although enalapril blocks the conversion of angiotensin I to angiotensin II, alternative pathways exist for the production of angiotensin II,[20] which may have been operative. Furthermore, elevated levels of angiotensin I, a smooth muscle cell mitogen,[21] may also have offset the beneficial effects of angiotensin II inhibition. Fourth, the lack of clinical efficacy may be due to the use of the wrong type of angiotensin-converting enzyme inhibitor; it is possible that the use of cilazapril, rather than enalapril, might be effective.

Although the restenosis rate of 53% and late loss in lumen diameter of 0.5 ± 0.8 mm in the present study strongly suggest a lack of beneficial effect, the true impact of combination drug therapy on restenosis can only be discerned through prospective randomized evaluation. In addition, since the sample size was chosen to detect a 50% reduction in late loss, a smaller beneficial effect may have been present but could not be detected. Finally, compliance to 3-drug therapy was determined by interview only and was not confirmed by more rigorous means such as counting pills, measuring enzyme activity, or screening for urine metabolites.

The combined administration of lovastatin, enalapril, and colchicine does not appear to inhibit restenosis after PTCA.

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Effects of Vitamin E on Endothelial Function in Men After Myocardial Infarction

Thomas G. Elliott, MBBS, Jacques D. Barth, MD, PhD, and G.B. John Mancini, MD

There is increasing evidence that oxidation of low-density lipoprotein (LDL) and abnormal endothelial function play important roles in atherogenesis.[1–4] Oxidized LDL itself has been shown to inhibit endothelium-dependent relaxation in animal models of atherosclerosis.[5,6] For these reasons, a role for antioxidant therapy in the treatment of endothelial dysfunction has been suggested. This study examines the effect of vitamin E on endothelial function in men who had previously had a myocardial infarction.

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Fourteen men who had experienced a myocardial infarction in the previous 3 to 6 months and recruited from a cardiac rehabilitation program and 12 healthy male hospital employees were studied. All subjects gave written informed consent to take part in the study, which was approved by the local institutional review board. All subjects had normal serum glucose and creatinine, were nonsmokers, and had had no acute medical conditions in the preceding 3 months. No subject had taken vitamin E, β carotene, and vitamin C on a regular basis within the previous 6 months. All post-myocardial infarction patients were studied between 3 and 6 months of either myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting, and continued to receive regular medication. No new medication was prescribed during the study period. All subjects were provided with 400 IU of vitamin E capsules of synthetic origin and were instructed to take 2 tablets/day.

With use of venous occlusion plethysmography,[7] forearm blood flow was measured at baseline and after 3 months of vitamin E therapy. Subjects were studied in the morning after resting supine for 20 minutes in a quiet clinical laboratory maintained at 21 to 23°C. Drugs were dissolved in 0.9% sodium chloride and were infused at 1.0 ml/min (Harvard Apparatus, South Natick, Massachusetts) into the brachial artery of the nondominant by way of an epidural catheter (Concord Portex, Keene, New Hampshire) sealed with dental wax to a 27-gauge dental needle (Sherwood Medical, St. Louis, Missouri). Drugs were infused in the following order: normal saline for 10 minutes, sodium nitroprusside (Roche, Basel, Switzerland) at 1, 3, and 10 μg/min for 6 minutes each, normal saline for 10 minutes, and acetylcholine (Iolab, Claremont, California) at 3, 10, and 30 μg/min for 4 minutes each. Blood flow was recorded during the last 3 minutes of each drug dose. Fasting blood samples for lipid analysis were drawn at baseline and after 3 months of vitamin E. Two-sided *t* tests were used to compare characteristics of the 2 groups. Analyses of variance for repeated measures were used to test for differences in blood flow during drug infusions.

Fourteen post-myocardial infarction subjects were enrolled and 12 completed the study. One patient who withdrew from the study underwent coronary artery bypass grafting, and the other was lost to follow-up. All 12 controls completed the study. At baseline, body mass index ($p = 0.018$), serum total cholesterol ($p = 0.023$), and triglycerides ($p = 0.028$) were higher in post-myocardial infarction patients than in controls and were unchanged after 3 months of vitamin E (Table I). In the noninfused arm, blood flow both at baseline and after vitamin E did not change significantly during the infusion of sodium nitroprusside or acetylcholine in either post-myocardial infarction patients or controls (data not shown). This observation confirmed that the infused

TABLE I Effect of Vitamin E on Endothelial Function in Post-Myocardial Infarction Patients

	Controls	Post-MI Subjects	
	At Entry (n = 12)	At Entry (n = 14)	After Vit. E (n = 12)
Age (yr)	46 ± 4	51 ± 2	
Body mass index (kg/m²)	24.4 ± 0.9	27.4 ± 0.8*	27.7 ± 1.1
Mean blood pressure (mm Hg)	99 ± 2	102 ± 2	100 ± 3
Total cholesterol (mM)	5.3 ± 0.2	6.1 ± 0.2*	5.8 ± 0.2
HDL cholesterol (mM)	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
Triglycerides (mM)	1.5 ± 0.3	2.0 ± 0.2*	2.0 ± 0.3

*p <0.05 compared with controls.
Values are expressed as mean ± SEM.
HDL = high-density lipoprotein; MI = myocardial infarction; Vit. = vitamin.

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A1594-1608

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Inter Partes Reexamination No. 95/001,096
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ELSEVIER

Pharmacology & Therapeutics 92 (2001) 165–178

Pharmacology & Therapeutics

Associate editor: J. Vinten-Johansen

Overview of therapies for prevention of restenosis after coronary interventions

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Abstract

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in the United States and across the world. The economic impact of CAD is staggering and on the rise. Percutaneous transluminal coronary angioplasty (PTCA) is widely used to treat severe, symptomatic coronary stenosis. The Achilles heel of angioplasty is restenosis of those treated arteries. As a result, numerous therapies, including mechanical and pharmacological approaches, to prevent restenosis have been studied. A greater understanding of the pathophysiology of restenosis has enhanced the success of these therapeutic approaches. To date, the most important and successful approach to limit restenosis has been the use of coronary stents. Stents have reduced the rate of restenosis from ~50% down to 20–30%. However, in-stent restenosis presents a new and an even more challenging dilemma. The success of adjunctive drug therapy has been promising, but, as of yet, very limited. Antithrombotic agents have reduced acute thrombosis and many of the acute complications of angioplasty. New approaches and therapies are very encouraging, and provide great hope in the treatment of restenosis. Brachytherapy has shown success in the treatment of in-stent restenosis, and recently has been approved by the United States Food and Drug Administration for this indication. Drug-eluting stents using antiproliferative drugs are the most exciting new advance in preventing restenosis, currently in Phase III trials. Gene therapy, targeted drug delivery, and newer antithrombotic agents are also under investigation. We will review the pathophysiology of restenosis, animal models, pharmacological therapies, and mechanical approaches for the treatment of restenosis. © 2001 Published by Elsevier Science Inc.

Keywords: Restenosis; Neointimal hyperplasia; Percutaneous transluminal coronary angioplasty; Coronary artery disease; Stent; Brachytherapy

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; NO, nitric oxide; PCI, percutaneous coronary intervention; PDGF, platelet-derived growth factor; PG, prostaglandin; PTCA, percutaneous transluminal coronary angioplasty; TX, thromboxane.

Contents

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0163-7258/01/$ – see front matter © 2001 Published by Elsevier Science Inc.
PII: S0163-7258(01)00168-1

1. Introduction

Coronary artery disease (CAD) is the most common cause of morbidity and mortality in the United States. According to the American Heart Association (2000), in 1997, there were 466,101 deaths attributed to CAD. It constitutes the largest health expenditure in the United States. Around the world, CAD is quickly becoming the most common cause of morbidity and mortality. The worldwide economic impact of coronary disease is staggering and is on the rise.

Percutaneous transluminal coronary angioplasty (PTCA) is widely used to treat patients with symptomatic CAD, which usually presents as angina (chest pain) or myocardial infarction. Approximately 450,000 coronary angioplasties were performed in the United States in 1997 (American Heart Association, 2000). Although usually initially successful, an angioplasty procedure can be complicated by a re-narrowing of the stenosis (restenosis) in 20–57% of the procedures (Holmes et al., 1984). Restenosis commonly occurs within 6 months of the angioplasty procedure. Commonly, patients who experience restenosis will have a recurrence of their symptoms (usually exertional chest pain), and will require another angioplasty procedure. The economic impact of treating restenosis is very high. An analysis of insurance claims in 1993 estimated the economic impact of treating coronary restenosis to be US$ ~1.6 billion annually in the United States (Topol et al., 1993).

2. Pathophysiology of restenosis

Restenosis following percutaneous coronary intervention (PCI) is very different from coronary atherosclerotic disease. Classical atherosclerotic coronary disease is characterized by a plaque containing varying amounts of lipid, calcification, and fibrosis. Atherosclerotic coronary disease is associated with the presence of hyperlipidemia, systemic arterial hypertension, tobacco use, diabetes, family history of coronary disease, and obesity. In contrast, restenosis is characterized histologically by neointimal formation (the appearance of cells and matrix in the intimal layer of the artery) and concentric compression of the outer layer of the blood vessel.

During PTCA, the balloon injures the arterial endothelium and, most importantly, the media (middle muscular layer) of the blood vessel. The high pressures used during balloon inflation commonly cause a rupture of the medial layer, usually at the junction of the plaque and the more normal segment of the artery. This causes tears or dissections within the artery, exposing deep layers of the media and the outer arterial layer (adventitia). The endothelial injury that occurs results in a loss of antithrombotic factors [e.g., nitric oxide (NO), prostaglandin $(PG)I_2$, and tissue plasminogen activator], and allows for platelet adhesion and aggregation. These platelets then degranulate releasing procoagulant factors [e.g., platelet-derived growth factor (PDGF), thromboxane $(TX)A_2$, adenosine diphosphate (ADP), etc.], leading to the formation of a deep intramural thrombus. This is then followed by proliferation and extracellular matrix synthesis by smooth muscle cells that have migrated in response to mechanical stretch injury, growth factor production, and disruption at the site of the balloon angioplasty, which ultimately leads to neointimal hyperplasia (Scott et al., 1996).

Although the mechanism of arterial injury during angioplasty appears to be widely accepted, there has been some debate over the mechanism of restenosis. In general, most investigators agree that the process of restenosis is associated with the healing response to the arterial injury from the angioplasty. Initial studies in rats suggested that the intimal and medial layers of the vessel were the major sites of the

restenotic process. However, these observations appear not to be applicable to clinical findings. Studies on the role of the adventitia in restenosis have suggested that this layer plays the key role in both the proliferation and the concentric compression of the external elastic lamina (negative remodeling) that defines restenosis (Scott et al., 1996). These findings have been corroborated by the experiments that demonstrated a beneficial effect of intracoronary radiation when the radiation energy was directed at the adventitia, but not when it was focused on the media.

3. Animal models

Animal models are crucial to the development of novel and effective human therapies. Extensive studies on the response to vascular injury were performed years before the development of angioplasty. These studies were primarily performed in the rat carotid artery, and utilized a very different type of injury. Instead of the medial rupture performed with noncompliant angioplasty balloons inflated to high pressures, a very compliant, low-pressure balloon was used to remove cells from the intima (denudation injury). These studies identified the intimal layer as the key site in the proliferative response seen with this type of injury. Unfortunately, clinical trials of agents that prevented the restenotic response to this injury in rats were ineffective in humans (Powell et al., 1989; Hermans et al., 1991).

An atherosclerotic rabbit model has also been used to model the arterial injury that occurs with angioplasty. In this model, rabbits are fed an atherosclerotic diet and then undergo denudation of the iliac arteries. A lesion then develops in the artery. This lesion is then injured with an angioplasty balloon. Although the restenotic lesions are somewhat dissimilar from human lesions, this model has provided valuable insights into the mechanism of repair after injury to an abnormal artery.

The most widely used and accepted model for studies on restenosis is the coronary overstretch balloon injury model in the pig. In this model, juvenile, domestic pigs (or miniswine) undergo an angioplasty procedure with the same equipment that is used clinically. The balloon is chosen so that its inflated diameter is larger than the diameter of the artery. Inflating this balloon causes a medial tear that is similar to what is seen clinically. In addition, the neointima formed in response to the balloon injury in the porcine model closely resembles the neointima seen in clinical samples. Despite the limitations of this model (juvenile pigs, normal arteries), success of an agent in the pig model generally correlates with clinical success.

4. Pharmacological therapy

Large numbers of clinical trials have investigated various drug therapies in an attempt to reduce the rate of restenosis. These pharmacological therapies can be divided into categories based on mechanisms of action; namely, prevention of thrombus formation, prevention of vascular recoil and remodeling, and prevention of inflammation and cell proliferation (Table 1). To date, no large-scale clinical trials of pharmacological therapy have demonstrated a significant reduction in the rate of restenosis. Some smaller trials have yielded promising results, and larger-scale trials are underway to validate these findings.

4.1. Prevention of thrombus formation

4.1.1. Antiplatelet agents

Following vessel injury, platelets begin to adhere to collagen and other substances within the vessel wall. This platelet adhesion is largely mediated by von Willebrand factor, which interacts with platelet glycoprotein Ib (part of the platelet membrane glycoprotein Ib–IX–V complex). These activated platelets release numerous contents from their granules, which ultimately lead to platelet aggregation. Platelet aggregation is mediated through the platelet membrane glycoprotein IIb/IIIa receptor, which principally binds fibrinogen. Fibrinogen cross-links platelets, forming the framework for a developing platelet-rich plug. This platelet-rich plug can lead to not only acute vessel closure, but also influences vascular smooth muscle cell migration and proliferation, which eventually can lead to restenosis (Ip et al., 1991). Numerous antiplatelet agents have been investigated in an attempt to reduce restenosis, including aspirin, ticlopidine, dipyridamole, cilostazol, TX inhibitors, prostacyclin analogues, and glycoprotein IIb/IIIa receptor inhibitors.

4.1.2. Aspirin

Aspirin acts by permanently inactivating PG G/H synthase, the first enzyme involved in the conversion of arachidonic acid to TXA_2. TXA_2 is a potent vascular smooth muscle vasoconstrictor and stimulates platelet aggregation. The Antiplatelet Trialists' Collaboration Investigators (1994) reviewed numerous randomized trials involving aspirin, demonstrating the benefit of aspirin in patients undergoing angioplasty.

4.1.3. ADP receptor antagonists

ADP receptor antagonists, such as ticlopidine and clopidogrel, differ from aspirin in that they do not affect the cyclo-oxygenase pathway. Their mechanism of action involves inhibition of the platelet 2-methylthio-ADP receptor, thus preventing ADP-induced platelet aggregation. As a secondary mechanism, they may also inhibit exposure of the fibrinogen-binding site of the platelet glycoprotein IIb/IIIa receptor.

The Stent Anticoagulation Restenosis Study (SARS) demonstrated that aspirin and ticlopidine were better than aspirin alone, or aspirin plus warfarin, for prevention of

Table 1
Trials of pharmacologic therapies for the prevention of restenosis

Agent or class	Therapeutic target	Proposed mechanism of action
Antiplatelet agents	Platelets	Prevent thrombus formation by interfering with platelet aggregation
Aspirin		
Ticlopidine/clopidogrel		
Dipyridamole		
Cilostazol		
Thromboxane inhibitors		
Prostacyclin analogues		
Glycoprotein IIb/IIIa receptor antagonists		
Anticoagulants		
Heparin	Thrombin/coagulation pathway	Prevent thrombus formation by blocking the coagulation pathway
Hirudin		
Coumadin		
Ca^{2+}-channel antagonists	Smooth muscle cells	Prevent vascular recoil and remodeling
ACE inhibitors	Endothelial and smooth muscle cells	Prevent vascular recoil and remodeling; possibly limit cell proliferation
NO	Endothelial cells	Prevent vascular recoil and remodeling
Serotonin receptor antagonists	Endothelial cells	Prevent vascular recoil and remodeling
Immunosuppressants and anti-inflammatory agents		
Corticosteroids	Smooth muscle cells	Prevent smooth muscle proliferation
Colchicine		
Tranilast		
Hydroxymethylglutaryl-coenzyme A reductase inhibitors	Multiple/smooth muscle cells	Prevent smooth muscle proliferation and limit atherosclerosis
Growth factor inhibitors		
Trapidil	Growth factors	Prevent smooth muscle proliferation
Antioxidants		
Probucol	Endothelial cells	Limit reactive oxygen species and lipid oxidation
Ascorbic		
α-Tocopherol		
β-Blockers	Endothelial and smooth muscle cells	Prevent vascular recoil and remodeling
Antibiotics	Bacteria and viruses that may contribute to restenosis	Inhibit the inflammatory response that may be initiated by an infection
Fish oils	Unknown	Limit PDGF and other cytokine production decreasing platelet aggregation and coronary spasm
Angiopeptin	Pituitary	Prevent neointimal proliferation by inhibiting growth hormone release
Antisense oligonucleotides	Growth factor genes	Limit smooth muscle and other cellular proliferation by inhibiting growth factors

stent thrombosis. However, there was no difference in long-term restenosis rates (Leon et al., 1998).

4.1.4. Dipyridamole

Dipyridamole acts as an antiplatelet medication by several mechanisms. It is a potent inhibitor of platelet aggregation. It stimulates prostacyclin synthesis and potentiates the action of prostacyclin (Moncada & Korbut, 1978). Dipyridamole blocks the reuptake of adenosine, a known vasodilator, leading to the accumulation of adenosine in the local vasculature (Gresele et al., 1986). Dipyridamole also inhibits phosphodiesterase, which increases platelet cyclic AMP levels, leading to platelet inactivation (Lam et al., 1982).

Schwartz et al. (1988) evaluated aspirin and dipyridamole in 375 patients after angioplasty. Restenosis rates at 6 months were equivocal. Intracoronary dipyridamole has also been studied, but it had negative results (Heidland et al., 1998).

4.1.5. Cilostazol

Cilostazol is a new antiplatelet medication that selectively blocks phosphodiesterase Type III. This blockade leads to an increased level of cyclic AMP within platelets, which results in decreased platelet activity and aggregation. In addition, studies have shown that cilostazol causes vasodilation and inhibits vascular smooth muscle cell proliferation (Takahashi et al., 1992).

A small, randomized study of 70 patients after stent implantation showed a significant decrease in restenosis rates at 6 months in the group treated with cilostazol (8.6% vs. 26.8%) (Kimishima et al., 1997). The Impact of Cilostazol on Restenosis After Percutaneous Coronary Balloon Angioplasty trial evaluated 211 patients taking cilostazol versus aspirin. The rate of angiographic restenosis was significantly lower in the cilostazol group than in the aspirin group (17.9% vs. 39.5%, $P < .001$). This was a randomized, prospective trial, but was not double-blinded and was carried out at a

single institution (Tsuchikane et al., 1999). Given these limitations, a large-scale, multicenter, double-blinded randomized trial will be needed to validate these results.

4.1.6. Thromboxane inhibitors

TXA_2 is one of the substances released by platelets in response to vascular injury. It stimulates platelet aggregation and causes vascular smooth muscle constriction and proliferation. By promoting thrombus formation, local vasoconstriction, and smooth muscle cell proliferation, TXA_2 may affect the restenosis process following angioplasty (Wilentz et al., 1987; Hanasaki et al., 1990). Aspirin achieves its antiplatelet effect by irreversibly inhibiting platelet cyclo-oxygenase, thus preventing production of TXA_2. Aspirin also inhibits endothelial cyclo-oxygenase and the subsequent production of prostacyclin. Although the inhibition of TXA_2 by aspirin is a desirable effect, the inhibition of prostacyclin production by aspirin may have adverse effects after angioplasty. Prostacyclin promotes vasodilation and inhibits platelet aggregation, benefits that are blunted by aspirin inhibition. Therefore, it is reasoned that more selective antagonists of TXA_2 may have a theoretical advantage following angioplasty (Oates et al., 1988).

In the Coronary Artery Restenosis Prevention on Repeated Thromboxane Antagonism Study (CARPORT), vapiprost, a TXA_2 receptor antagonist, was randomized against placebo. Follow-up data at 6 months showed that vapiprost did not prevent restenosis or reduce adverse clinical events (Rensing et al., 1993). The Multi-Hospital Eastern Atlantic Restenosis Trial II (M-HEART II) evaluated sulotroban, another TXA_2 receptor antagonist, against aspirin and placebo, and demonstrated no reduction in restenosis at 6 months (Savage et al., 1995).

4.1.7. Prostacyclin analogues

Prostacyclin (epoprostenol, PGI_2) exerts effects opposite to those of TX, causing vasodilation and platelet inhibition. In addition, prostacyclin displays an antiproliferative effect (Shirotani et al., 1991). These properties of prostacyclin have led to trials to evaluate its use in the prevention of restenosis.

Gershlick et al. (1994) randomized 135 patients to epoprostenol or buffer before angioplasty that was then continued for 36 h after the procedure. No reduction in restenosis was observed at 6 months. Several other small studies have investigated prostacyclin, but none have been able to show a reduction in restenosis (Knudtson et al., 1990; Darius et al., 1992).

4.1.8. Glycoprotein IIb/IIIa receptor antagonists

Glycoprotein IIb, together with glycoprotein IIIa, forms the platelet fibrinogen receptor, which is the final pathway of platelet aggregation. The Evaluation of Abciximab for the Prevention of Restenosis (EPIC) trial evaluated the glycoprotein IIb/IIIa receptor antagonist abciximab in high-risk patients undergoing angioplasty. The abciximab group had a 26% reduction in clinical restenosis at 6 months. However, restenosis was not a primary endpoint of this study, and routine angiographic follow-up was not performed (Topol et al., 1994). Since then, trials with eptifibatide (IMPACT-II) (Tardiff et al., 1999), tirofiban (RESTORE) (Gibson et al., 1998), and abciximab (ERASER) (The ERASER Investigators, 1999) have included angiographic follow-up and have shown no reduction in restenosis rates. Since then, data regarding the use of oral glycoprotein IIb/IIIa inhibitors has come forth. The Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial randomized 7232 patients to oral xemilofiban 10–20 mg or placebo for up to 182 days, and showed no decline in restenosis (O'Neill et al., 2000).

4.1.9. Anticoagulants

4.1.9.1. Heparin. Heparin is not a single structure, but rather, a family of mucopolysaccharide chains of varying composition. Heparin forms a complex with antithrombin III, giving rise to its anticoagulant properties. Heparin has been shown to reduce neointimal proliferation and restenosis following vascular injury in experimental models.

The Subcutaneous Heparin and Angioplasty Restenosis Prevention (SHARP) trial randomized 339 patients to subcutaneous heparin versus no therapy. Follow-up data at 4 months showed no difference in clinical outcomes or restenosis rates (Brack et al., 1995). The Enoxaparin Restenosis Trial (ERA) (Faxon et al., 1994), the Reviparin in Percutaneous Transluminal Coronary Angioplasty (REDUCE) trial (Karsch et al., 1996), Fraxiparine Angioplastie Coronarie Transluminale (FACT) study (Lablanche et al., 1997b), and the Ardeparin and Restenosis Study Group (Gimple et al., 1999) all evaluated low-molecular-weight heparins versus placebo. None of these trials were able to demonstrate a reduction in restenosis.

4.1.9.2. Hirudin. Hirudin is a small compound that is a direct thrombin inhibitor. The advantage of hirudin over other anticoagulants is its ability to block thrombin at multiple sites, without the need for circulating antithrombin III. Its small size allows hirudin to inhibit clot-bound thrombin and to prevent further thrombus formation (Weitz et al., 1990). Animal studies with hirudin have demonstrated a reduction in restenosis rates (Sarembock et al., 1991).

The Hirudin in a European Trial Versus Heparin in the Prevention of Restenosis After PTCA (HELVETICA) study randomized 1141 patients to a 24-h heparin infusion, a 24-h hirudin infusion, or 3 days of subcutaneous heparin following angioplasty. While early ischemic events were reduced in the hirudin group, there was no long-term difference in restenosis (Serruys et al., 1995). The Hirulog Angioplasty Study randomized 4098 patients to bivalirudin or heparin during angioplasty. Angiographic follow-up in 244 of these patients showed no difference in restenosis between the two groups (Burchenal et al., 1998).

4.1.9.3. Coumadin. Coumadin exerts its anticoagulant effect by inhibiting vitamin K epoxide reductase, and possibly vitamin K reductase. This limits carboxylation of the vitamin K-dependent coagulant proteins; namely, prothrombin, factor VII, factor IX, and factor X. Coumadin also limits the carboxylation of protein C and protein S, limiting their regulatory function in the coagulation cascade (Fasco et al., 1982).

Two small studies evaluating coumarins concluded that oral anticoagulants were not more effective than aspirin after angioplasty. However, therapeutic prothrombin times were not reported in one of these trials and were only 35% in the other (Thornton et al., 1984; Urban et al., 1988). The Balloon Angioplasty and Anticoagulation Study (BAAS) randomized 1058 patients to coumarins in addition to aspirin versus aspirin alone for 6 months after angioplasty. The group with coumarins plus aspirin had a higher event-free survival (composite endpoint of death, myocardial infarction, target-lesion revascularization, and stroke) than the group with aspirin alone (86% vs. 80%, $P=.01$). However, there was no information on restenosis rates (ten Berg et al., 2000).

4.2. Prevention of vascular recoil and remodeling

4.2.1. Ca^{2+}-channel antagonists

Ca^{2+}-channel antagonists have been considered for prevention of restenosis due to their ability to reduce elastic recoil and smooth muscle cell vasoconstriction (Ferrari, 1996). Several controlled studies have examined Ca^{2+}-channel blockers in the prevention of restenosis. The Coronary Angioplasty Amlodipine Restenosis Study (CAPARES) randomized 635 patients to amlodipine versus placebo. Although amlodipine did not reduce restenosis rates, the composite major adverse clinical events were reduced in the amlodipine group (Jorgensen et al., 2000).

Individual trials evaluating nifedipine, verapamil, and diltiazem have not been able to demonstrate a decrease in the rate of restenosis (Whitworth et al., 1986; Hoberg & Kubler, 1991; O'Keefe et al., 1991). However, a meta-analysis of five randomized trials involving 919 patients showed that patients treated with Ca^{2+}-channel antagonists had a 32% relative reduction in the angiographic restenosis compared with controls (odds ratio = 0.68; confidence interval 0.49–0.94, $P=.03$) (Hillegass et al., 1994). The routine use of Ca^{2+}-channel antagonists for prevention of restenosis has not been widely accepted, in part because some data have shown an increased incidence of ischemic events with the use of Ca^{2+}-channel antagonists following myocardial infarction.

4.2.2. Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors block the effects of angiotensin II, which is a potent vasoconstrictor. In addition to its vasoconstricting properties, angiotensin also stimulates vascular smooth muscle proliferation (Daemen et al., 1991). Thus, ACE inhibitors could be considered under two categories for prevention of restenosis: (1) prevention of vascular recoil and remodeling and (2) prevention of inflammation and cell proliferation.

The Multicenter American Research Trial With Cilazepril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MARCATOR) demonstrated no reduction in the rate of restenosis with the use of cilazepril at 24 weeks. There was also no reduction in clinical outcomes, including myocardial infarction, coronary artery bypass surgery, angina, and need for repeat coronary angioplasty (Faxon, 1995). The Multicenter European Research Trial With Cilazepril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR), a similar trial in Europe using lower doses of cilazepril, found similar results (The MERCATOR Investigators, 1992). Desmet et al. (1994) evaluated fosinopril in 304 patients against placebo following angioplasty and showed no reduction in restenosis rates.

4.2.3. Nitric oxide (NO)

NO plays an important role in the regulation of vascular tone in the endothelium. It is released by normal endothelium and causes vasodilation (Palmer et al., 1987). In addition to its vasodilatory effects, NO has other properties that could also alter the process of restenosis. NO has been shown to decrease platelet adhesion and aggregation, to serve as a scavenger of superoxide anions, and to beneficially affect vascular remodeling (Clancy et al., 1992; Groves et al., 1993; Gibbons & Dzau, 1994).

The Angioplastic Coronaire Corvasal Diltiazem (ACCORD) trial evaluated 700 patients with infusion of linsidomine followed by oral molsidomine (direct NO donors) versus diltiazem. Results showed a modest improvement in the 6-month restenosis results (38% vs. 46.5%, $P=.026$) that was mainly due to an improved immediate angioplasty result. Late lumen loss did not differ significantly between the two groups (Lablanche et al., 1997a).

4.2.4. Serotonin receptor antagonists

Serotonin is one of the products released from aggregating platelets following endothelial injury. Serotonin can affect restenosis through platelet activation, smooth muscle cell proliferation, and vasoconstriction. Alone, serotonin is a weak platelet inhibitor, but it potentiates the activity of other platelet agonists, such as TXA_2, ADP, catecholamines, and thrombin, thus amplifying the effects of platelet aggregation (De Clerck & Janssen, 1990). Animal studies demonstrate that serotonin can induce vascular smooth muscle cell proliferation (Nemecek et al., 1986). Serotonin can cause both vasoconstriction and vasodilation, depending on the type of receptor. Antagonists to serotonin such as ketanserin can block some of the vasoconstricting effects.

The Post Angioplasty Restenosis Ketanserin (PARK) trial evaluated ketanserin, a serotonin antagonist, in the prevention of restenosis after coronary angioplasty. Clinical

follow-up of 525 patients at 6 months showed no reduction in clinical endpoints or restenosis rates of ketanserin over placebo (Serruys et al., 1993).

4.3. Prevention of inflammation and cell proliferation

4.3.1. Immunosuppressants and anti-inflammatory agents

Vascular smooth muscle cell proliferation contributes to restenosis following angioplasty. The migration and proliferation of smooth muscle cells in response to endothelial injury is induced by cytokines. Smooth muscle cells migrate from the media into the intima and result in neointimal hyperplasia with cellular proliferation and extracellular matrix production. Agents that prevent the migration and proliferation of smooth muscle cells may help prevent restenosis. However, the use of these antiproliferative agents must be balanced against potential organ toxicity. The use of the more potent antineoplastic agents has been limited by life-threatening side effects. Corticosteroids, colchicine, and tranilast are some of the antiproliferative agents that have been studied in the prevention of restenosis and they are discussed below.

4.3.1.1. Corticosteroids. Corticosteroids have been studied in the prevention of restenosis because of their known immunosuppressive effects. Corticosteroids inhibit smooth muscle cell proliferation and produce a variety of anti-inflammatory effects, the mechanisms of which remain only partially understood (Cherva et al., 1989). The largest trial to date evaluating corticosteroids was the M-HEART randomizing 915 patients to 1 g of methylprednisolone versus placebo within 24 h prior to angioplasty. Follow-up data at 6 months showed no reduction in restenosis (Pepine et al., 1990).

4.3.1.2. Colchicine. Colchicine, which causes metaphase arrest of cell division, has been shown to limit restenosis in experimental models (Bauriedel et al., 1994). Colchicine has also been studied in clinical trials. O'Keefe et al. (1992) evaluated 197 patients with colchicine (0.6 mg b.i.d.) versus placebo for 6 months following angioplasty and found no reduction in restenosis. A small study of 50 patients using colchicine together with lovastatin and enalapril also showed no benefit (Freed et al., 1995).

4.3.1.3. Tranilast. Tranilast, *N*-(3′4′-dimethoxycinnamoyl)-anthranilic acid (*N*-5), has been used as an allergy medication, due to its effect of suppressing mast cell degranulation (Azuma et al., 1976). It also interferes with vascular smooth muscle cell migration and proliferation by suppressing the production of cytokines, such as PDGF, transforming growth factor-β1, and interleukin-1 (Takahashi et al., 1999). This effect of tranilast has led to trials regarding restenosis prevention.

The Tranilast Restenosis Following Angioplasty Trial (TREAT) randomized 255 patients to either 600-mg tranilast per day, 300-mg tranilast per day, or placebo for 3 months following angioplasty. Restenosis rates were 14.7% in the 600-mg group, 35.2% in the 300-mg group, and 46.5% in the placebo group (Tamai et al., 1999). Other small trials have also shown favorable results with tranilast following angioplasty or stent placement (Kosuga et al., 1997; Ishiwata et al., 2000). The Prevention of Restenosis with Tranilast and Its Outcomes (PRESTO) trial is currently underway to evaluate tranilast in 11,500 patients following angioplasty (Holmes et al., 2000).

4.3.2. Hydroxymethylglutaryl-coenzyme A reductase inhibitors

Experimental evidence suggests that hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) may exert a direct inhibitory effect on proliferating myocytes, independent of any lipid-lowering action. In addition, statin therapy has been shown to inhibit platelet aggregation (Lacoste et al., 1995), reduce inflammatory responses of the vascular wall (Williams et al., 1998), and improve coronary endothelial function (Treasure et al., 1995). These properties of statins have led to clinical trials evaluating these agents in restenosis prevention.

The Fluvastatin Angioplasty Restenosis (FLARE) trial evaluated high-dose fluvastatin versus placebo in 1054 patients following angioplasty. Fluvastatin reportedly exerts more neointimal suppressant effects than other statins. Although there was a reported reduction in mortality and myocardial infarction in the fluvastatin treatment group, there was no difference in the rate of restenosis at 40 weeks (Serruys et al., 1999). Two earlier smaller trials, the Prevention of Restenosis by Elisor After Transluminal Coronary Angioplasty (PREDICT) study using pravastatin (Bertrand et al., 1997) and the Lovastatin Restenosis Trial Study Group (Weintraub et al., 1994), also failed to show a reduction in restenosis. Recently, statins have been evaluated in patients after stent placement. In a retrospective, nonrandomized trial evaluating 525 patients following stent placement, the group of patients taking statins (258 patients) had a significant decrease in restenosis (25.4% vs. 38%) at 6 months compared with those not taking statins (267 patients) (Walter et al., 2000). It may be that statins have a role in patients after stent implantation where restenosis is almost entirely due to neointimal hyperplasia. Further investigation with a randomized, controlled trial is warranted.

4.3.3. Growth factor inhibitors

Trapidil is an antiplatelet agent that is both a TXA_2 inhibitor and a PDGF inhibitor. PDGF is one of the mediators of the inflammatory response following angioplasty. It is released by damaged epithelial cells and platelets, and it stimulates proliferation of several cell lines, including vascular smooth muscle cells. Animal studies using the PDGF antagonist trapidil have demonstrated that trapidil decreases neointimal smooth muscle cell proliferation following angioplasty (Ferns et al., 1991).

Initial clinical studies with trapidil have shown positive results. A small study by Okamoto et al. (1992) found a statistically significant reduction in restenosis in 36 patients treated with trapidil (200 mg t.i.d.) (19%) versus 36 patients treated with aspirin plus dipyridamole (42%). The Studio Trapidil Versus Aspirin Nella Restenosis Coronica (STARC) was a multicenter trial evaluating 254 patients with trapidil (100 mg t.i.d.) versus aspirin (100 mg t.i.d.) for 6 months following angioplasty. There was a significant decrease in the rate of restenosis in the trapidil group (24.2%) compared with the aspirin group (Maresta et al., 1994). Given these encouraging results, further evaluation of trapidil with a large-scale trial is warranted.

4.3.4. Antioxidants

Oxidative stress is increasingly recognized as an important factor in atherosclerosis and restenosis. The generation of reactive oxygen species and oxygenation of lipids impairs endothelial function. Oxidized lipoprotein inhibits the release of NO from endothelial cells. In addition, oxidative stress exerts toxic effects on vascular smooth muscle cells, leading to the activation of monocytes and macrophages, which initiates a cascade of inflammatory responses (Berliner et al., 1995).

Several compounds, including probucol, ascorbic acid, and α-tocopherol, have been shown to reduce intimal hyperplasia in animal models. However, no large-scale clinical trials have been able to demonstrate a reduction in restenosis. Small studies have suggested that probucol started before angioplasty may prevent restenosis. The Multivitamins and Probucol (MVP) study evaluated 317 patients with one of four treatments: placebo, 500-mg probucol, multivitamins (30,000-IU β-carotene, 500-mg vitamin C, and 700-IU vitamin E), or probucol plus multivitamins. All therapies were initiated 1 month before the planned angioplasty. Rates of restenosis were decreased by 47% in patients treated with probucol (Tardif et al., 1997). The Probucol Angioplasty Restenosis Trial (PART) evaluated 101 patients after angioplasty, and demonstrated a significant reduction in restenosis (23% with probucol vs. 58% with placebo). However, patients required pretreatment with probucol for 30 days (Yokoi et al., 1997). In another study of 118 patients, Watanabe et al. (1996) found a 40% reduction in restenosis in patients treated with probucol. Patients were pretreated with probucol for 1 week. To date, every trial showing a beneficial effect of probucol has required pretreatment of at least 1 week. When no pretreatment was used in one previous trial, probucol had no beneficial effect (O'Keefe et al., 1996). The period of pretreatment required has not been defined. Based on these findings, further investigation with a larger randomized trial is warranted.

4.3.5. β-Blockers

Carvedilol is a nonselective β-blocker used in the treatment of CAD, heart failure, and hypertension. In addition to its nonselective adrenergic receptor blockade, carvedilol and its metabolites are antioxidants with much more potent effects than probucol or vitamin E (Yue et al., 1994). Carvedilol is also a direct inhibitor of vascular smooth muscle cell migration and proliferation (Sung et al., 1993). Given these latter properties, carvedilol has been studied as a possible inhibitor of restenosis.

The European Carvedilol Atherectomy Restenosis (EUROCARE) trial evaluated 406 patients randomized to carvedilol (25 mg b.i.d.) versus placebo. Results showed that carvedilol failed to reduce restenosis after atherectomy (Serruys et al., 2000).

4.3.6. Antibiotics

Some studies suggest that infectious processes contribute to atherosclerosis. The organism most frequently implicated is *Chlamydia pneumoniae*, a common cause of respiratory tract infections. *Chlamydia* has been detected in atherosclerotic plaques, although a direct causal relationship of *Chlamydia* on atherosclerosis has yet to be proven (Muhlestein et al., 1996). Roxithromycin is a macrolide antibiotic with activity against *C. pneumoniae*. It has been hypothesized that eradication of chronic chlamydial infections may attenuate the inflammatory response within the arterial wall, leading to a reduction in restenosis (Agen et al., 1993). Roxithromycin also exhibits intrinsic antioxidant activity, which could also affect the restenosis process.

The Intracoronary Stenting and Antibiotic Regimen (ISAR-3) trial randomized 1010 patients undergoing stent placement to 4 weeks of roxithromycin (300-mg q.i.d.) versus placebo. Follow-up data after 6 months showed no difference in restenosis rates between the two groups (Neumann et al., 2001).

4.3.7. Fish oils

A low rate of CAD exists among the Eskimo population, a group that consumes a diet rich in fish oils (Bang et al., 1976). Studies have demonstrated that omega-3 polyunsaturated fatty acids from fish decrease the synthesis of PDGF and other cytokines that promote vascular smooth muscle cell proliferation (Simopoulos, 1997). Also, increases in the levels of omega-3 polyunsaturated fatty acids in cell membranes alter eicosanoid production, which may lead to decreased platelet aggregation and coronary spasm (Leaf & Weber, 1988).

Multiple trials have evaluated omega-3 polyunsaturated fatty acids for possible prevention of restenosis. A meta-analysis of several early trials suggested a reduction in the rate of restenosis (Goodnight et al., 1992). These trials were limited by small size, differences in dosing methods, and differences in definitions of restenosis. Two subsequent larger trials have yielded negative results. The Fish Oil Restenosis Trial (FORT) was a multicenter trial in the United States evaluating 503 patients, and showed no reduction in restenosis at 6 months (Leaf et al., 1994). The Enoxaparin and Maxepa for the Prevention of Angio-

plasty Restenosis (EMPAR) trial in Canada evaluated fish oils and enoxaparin in a 2 × 2 factorial design. Eight hundred fourteen patients were evaluated for 18 weeks following angioplasty. Both enoxaparin and fish oils showed no decrease in restenosis (Cairns et al., 1996).

4.3.8. Angiopeptin

Angiopeptin is a somatostatin analogue that inhibits growth hormone release. It also has an antiproliferative effect on neoplastic cells in cell culture, through the inhibition of growth factors (Pan et al., 1992). Also, in animal models, angiopeptin has been shown to inhibit neointimal proliferation and limit restenosis (Hong et al., 1993; Santoian et al., 1993).

Human studies have yielded conflicting results. A small trial of 112 patients randomized to a 5-day infusion of angiopeptin versus placebo showed a reduction in restenosis (12% with angiopeptin vs. 40% with placebo) (Eriksen et al., 1995). Emanuelsson et al. (1995) randomized 553 patients to a 5-day subcutaneous infusion of angiopeptin versus placebo. While there was a decreased incidence of clinical events, no significant effect was seen in regard to restenosis. Inconvenience of drug delivery, as well as a lack of benefit in prevention of restenosis from the larger trials, has dampened enthusiasm for angiopeptin.

4.3.9. Antisense oligonucleotides

Attempts are underway to target gene expression of various growth factors involved in restenosis. Antisense is a method to inhibit gene expression by using short sequences of DNA that are complementary to messenger RNA. Several antisense oligonucleotides have been studied in animal models. In fact, intracoronary administration of c-myc antisense has been performed in 16 patients undergoing angioplasty to demonstrate safety (Lee et al., 1999). At present, there are still many problems that need to be solved in order to make antisense therapy a viable option in the prevention of restenosis. Future studies will depend on the development of effective carrier systems, techniques to stabilize agents, improved cellular uptake, and target specificity.

5. Coronary stents

The advent of coronary stents represents a major advance in the continuing battle with the problem of restenosis. Stents have significantly reduced the incidence of restenosis and are the only United States Food and Drug Administration-approved device for the treatment of restenosis. In the STRESS trial, stenting was associated with a lower 6-month incidence of both restenosis (32% vs. 42%) and of revascularization via surgery or repeat angioplasty (10% vs. 15%) (Fischman et al., 1994). The BENESTENT trial showed similar beneficial results (Serruys et al., 1994). Despite this initial benefit, the long-term value of stenting remains uncertain.

Stents exert their effect through purely mechanical means. They provide luminal scaffolding that virtually eliminates recoil and remodeling. However, coronary stenting does not eliminate the problem of restenosis. Patients receiving new stents have a 20–30% chance of restenosis. Stents do not decrease and actually increase the proliferative component of restenosis (Edelman & Rogers, 1998). The vascular response to stenting is slightly different than that observed with angioplasty alone. It is more chronic, and involves a greater degree of injury, leading to more pronounced neointimal lesions (Edelman & Rogers, 1998). The majority of restenosis following stenting develops within the first 3–4 months after the procedure; lumen narrowing is usually completed by 6 months (Mehran et al., 1999). In-stent restenosis represents another challenge that is currently under investigation.

6. Brachytherapy

Intracoronary radiation is the most promising new therapy for the treatment of restenosis following PCI. Intracoronary radiation, both γ and β, has been shown to reduce neointimal hyperplasia in the porcine model and, as a result, to markedly reduce restenosis after balloon angioplasty (Wiedermann et al., 1994; Waksman et al., 1995a, 1995b; Mazur et al., 1996).

Radiation therapy provides a nonpharmacological approach to controlling the response to injury and unfavorable remodeling that occurs after PCI. This is analogous to its role in limiting the growth of many rapidly proliferating neoplasms. The main effect of vascular radiotherapy is breaking single- and double-stranded DNA and, thereby, killing actively dividing cells in the media, intima, and adventitia (Brenner et al., 1996). Radiation may also injure the dormant cells located in the media and adventitia that will be stimulated to migrate, proliferate, and synthesize matrix after the coronary intervention. Wilcox et al. (1996) also showed that radiation inhibits the expression of PDGF-α and PDGF-β receptor mRNA after angioplasty in the adventitial cells, thereby inhibiting the recruitment and proliferation of adventitial myofibroblasts in the porcine model.

Recent clinical trials have demonstrated a reduction in neointimal hyperplasia after intracoronary radiation with doses of 10–30 Gy of ionizing radiation delivered by either [β]- or [γ]-emitters to injured vessels. The Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) trial was the first attempt at catheter-based brachytherapy to reduce restenosis in a prospective double-blinded randomized study. The SCRIPPS-I trial enrolled 55 patients between March and December of 1995, and resulted in a dramatic decrease in the rate of restenosis when ^{192}Ir brachytherapy was employed. The initial benefit in reducing the restenosis rate has been maintained up to a 3-year follow-up (Teirstein et al., 1999, 2000). Subsequently, the Washington Radiation In-Stent Restenosis Trial (WRIST)

with 130 patients yielded results similar to the SCRIPPS-I trial. GAMMA-I was the first multicenter, double-blind, randomized trial with 252 patients enrolled at 12 medical centers in the United States.

β-Energy catheter systems are also effective in preventing restenosis. King et al. (1998) demonstrated efficacy of a β-catheter system in a small safety study. Raizner et al. (2000) showed that a β wire system could effectively inhibit restenosis in a randomized clinical trial.

These studies have elucidated the definitive role of brachytherapy in preventing or reducing restenosis after angioplasty. Several other multicenter randomized trials; namely, BETA-CATH, START, INHIBIT, BRIE, etc., are awaiting conclusion and final analysis (Waksman, 2000).

7. Drug-eluting stents

The most intriguing new therapy is a series of recently developed stents coated with antiproliferative drugs. The drug coatings under investigation include sirolimus, rapamycin, actinomycin D, and paclitaxel. Sirolimus is a potent immunosuppressive agent. It binds to an intracellular receptor and elevates p27 levels, leading to an inhibition of cyclin/cyclin-dependant kinase complexes and ultimately inducing cell-cycle arrest. Rapamycin is a cytostatic drug that induces late G1 cell-cycle arrest. Taxol binds to microtubules and arrests cells during mitosis. Actinomycin D prevents RNA synthesis by binding DNA.

A number of studies are currently underway to evaluate the benefit and safety of these coated stents in the prevention of restenosis. The early data are very encouraging. Sousa et al. (2001) recently published a report of 30 patients randomized to sirolimus-coated stents showing minimal, if any, intimal hyperplasia using intravascular ultrasound (IVUS) follow-up after 6 months.

8. Conclusion

Restenosis remains a major limitation in the long-term success of PTCA. Early trials with numerous pharmacological and mechanical devices have been disappointing. The advent of coronary stenting provided a major advancement in our therapy. Newer therapies are proving more effective, and have great potential. Brachytherapy is the most encouraging advance of all the newer therapies since the advent of stents. United States Food and Drug Administration approval of this technique has been granted recently. Other therapies that have shown promising preliminary results include drug-eluting stents; gene therapy; targeted drug therapy and newer antithrombotic agents; and, ultimately, one or more of the above therapies may provide the answer. Thus, there is renewed enthusiasm for the potential to eventually eliminate restenosis.

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Br Heart J 1994;71:7–15

Failure of epoprostenol (prostacyclin, PGI_2) to inhibit platelet aggregation and to prevent restenosis after coronary angioplasty: results of a randomised placebo controlled trial

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Abstract

***Objective*—To study the effect of epoprostenol (prostacyclin, PGI_2) given before, during, and for 36 h after coronary angioplasty on restenosis at six months and to evaluate the transcardiac gradient of platelet aggregation before and after percutaneous transluminal coronary angioplasty (PTCA) in treated and placebo groups.**

***Design*—Double blind placebo controlled randomised study.**

***Patients*—135 patients with successful coronary angioplasty.**

***Methods*—Intravenous infusion of PGI_2 (4 ng/kg/ml) or buffer was started before balloon angioplasty and continued for 36 hours. Platelet aggregation was measured in blood from the aorta and coronary sinus before and after PTCA in each group. Routine follow up was at six months with repeat angiography and there was quantitative assessment of all angiograms (those undertaken within the follow up period and at routine follow up).**

***Presentation of results*—Restenosis rates in treated and placebo groups determined according to the National Heart, Lung and Blood Institute definition IV. Comparison at follow up between the effect of treatment on mean absolute luminal diameter and mean absolute follow up diameter in the placebo group. Comparison of acute gain and late loss between groups.**

***Results*—Of 125 patients available for assessment 23 were re-admitted because of angina within the follow up period. Quantitative angiography showed restenosis in 15 (10 in the PGI_2 group and five in the placebo group). Of 105 patients evaluated at six month angiography there was restenosis in nine more in the PGI_2 group and 18 more in the placebo group. Total restenosis rates (for patients) were 29·2% for PGI_2 and 38·3% for placebo (NS). The mean absolute gain in luminal diameter was 1·84 (0·76) mm in the PGI_2 group and 1·58 (0·56) mm in the placebo group ($p = 0·04$); the late loss in the PGI_2 group was also greater (0·65 (0·94) mm *vs* 0·62 (0·89) mm (NS) and there was no significant difference in final luminal diameter at follow up between the two groups (1·83 (0·88) mm *v* 1·59 (0·60) mm). The transcardiac gradient of quantitative platelet aggregation increased after PTCA in both groups, indicating that PGI_2 in this dose did not affect angioplasty-induced platelet activation. Mean (SD) platelet activation indices in the PGI_2 group were pre PTCA aorta 8·4 (4·1) *v* coronary sinus 8·8 (4·0) ($p = 0·001$) and post PTCA aorta 8·9(3·0) *v* coronary sinus 12·9 (5·7) ($p = 0·001$). In the placebo group the values were pre PTCA aorta 7·6 (3·3) *v* coronary sinus 7·4 (3·6) ($p = 0·001$) and post PTCA aorta 7·6(2·8) *v* coronary sinus 11·2(4·3) ($p = 0·001$).**

***Conclusion*—The dose of PGI_2 given was designed to limit side effects and as a short-term infusion did not significantly decrease the six month restenosis rate after PTCA. The sample size, which was determined by the original protocol and chosen because of the potency of the agent being tested, would have detected only a 50% reduction in restenosis rate. There was, however, no effect in the treated patients on the increased platelet aggregation seen in placebo group as a result of angioplasty. Angioplasty is a powerful stimulus to blood factor activation. Powerful agents that prevent local platelet adhesion and aggregation are likely to be required to reduce restenosis.**

(*Br Heart J* 1994;71:7–15)

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Accepted for publication 6 July 1993

Restenosis after angioplasty occurs as a consequence of an over response of the vessel wall to balloon damage. The procedure itself causes considerable damage to the artery[1,2] with loss of endothelial cells and disruption of the intima and media. Experimental models have shown that platelets adhere to the damaged surface within a few minutes.[3,4] Adherence, activation, and α granule release of growth factors for smooth muscle cells are a well recognised sequence[5,6] and smooth muscle cell intimal hyperplasia is acknowledged to be the cause of restenosis in the 70% or so of cases not caused by recoil,[7] as shown by necropsy[10,11] and in atherectomy-retrieved samples from lesions that have restenosed.[12]

A normal endothelium protects against the unwanted interaction between platelets and subendothelial platelet-adhering collagen and

microfibrils. It acts both as a physical and chemical barrier partly through its high concentration of prostacyclin (PGI_2) which is the most powerful antiaggregating substance known.[13] PGI_2 is concentrated in the endothelial layer[14] and acts by increasing platelet cAMP which in turn inhibits intraplatelet activation metabolic pathways.[15,16] Balloon angioplasty, by removing the endothelial layer, will diminish the concentration of locally produced prostacyclin. Infused into normal volunteers PGI_2 has been shown to have antiplatelet effects.[17] Prostacyclin (as epoprastenol, PGI_2) therefore seems to be a good candidate for reducing the incidence of restenosis after coronary angioplasty.

We assessed the effect of epoprostenol (PGI_2) administered intravenously, during and for 36 hours after PTCA, on quantitatively determined restenosis. Any effect of PGI_2 on changes in transcardiac platelet function measured during angioplasty was also evaluated.

Patients and methods

All patients undergoing angioplasty at the London Chest Hospital were considered for inclusion in the trial, with the exception of those with total coronary occlusion, restenosis, after previous angioplasty, or vein graft lesions. The trial was approved by the ethics committee of the National Heart and Brompton Hospitals.

After formal consent patients were randomly allocated to received either PGI_2 infusion, made up in buffer to permit an infusion rate of 4 ng/kg/min, or buffer alone. Patient and operator were blinded to the randomisation group. The PGI_2 was made up by the pharmacy department from stored material provided by Wellcome.

ANGIOPLASTY PROCEDURE

All patients received 300 mg aspirin with their premedication. After a femoral artery sheath was in place, blood pressure was recorded and the infusion was started provided the systolic blood pressure was >110 mm Hg. Heparin 10 000 U and diazepam 5 mg were given via the femoral vein sheath, as was the routine clinical practice. A 7 F NIH catheter was passed via the femoral vein into the coronary sinus in order to obtain blood samples for platelet aggregometry and measurement of 6 keto $PGF_{1\alpha}$ (the stable metabolite of PGI_2). Dye visualisation was used to place the catheter as close as possible to the vein draining the target artery (great cardiac vein for the left anterior descending coronary artery; middle or posterior cardiac vein for the circumflex and right coronary arteries). Once the infusion had been running for a minimum of 10 minutes the chosen guiding catheter was placed in the aortic root close to but not engaged in the coronary artery.

ASSESSMENT OF PLATELET FUNCTION

After 5 ml of blood had been drawn from the coronary sinus catheter, and discarded 4·5 ml was carefully taken into a test tube containing 0·5 ml trisodium citrate (TSC). This was sample CS1. Another 4·5 ml blood sample (designated A1) was taken from guiding catheter in the aortic root (and placed in a further 0·5 ml TSC). The angioplasty was then performed according to operator's choice of wire, balloon, inflation pressure, and inflation times. During this time the coronary sinus catheter was carefully hand flushed with heparinised saline every half hour.

Immediately after established angiographic success, further blood samples were taken as before from the catheter in the coronary sinus (CS2) and from the guiding catheter which had been disengaged from the coronary artery but left close to its origin (A2). All samples were processed within two hours of withdrawal. Samples for 6-keto-$PGF_{1\alpha}$ were stored at −70°C for radioimmunoassay. Samples for aggregometry were transferred to the haematology laboratory, the platelet count was standardised to 200 × 10^9/l with platelet poor plasma, and analysed without delay. To ensure platelet viability we discarded any samples that could not be measured within 2 h of collection, because of a prolonged PTCA procedure, for example. We assessed aggregability by calculating a dose response curve to ADP[18]—that is, the slope produced by plotting the initial aggregation slope against the log concentration of ADP required to produce that slope for final concentrations of ADP of 20 μM, 10 μM, 5 μM, 2·5 μM, and 1·25 μM ADP. The value of the slope produced is the platelet activation index (PAI).[18] Blood concentrations of 6-keto-$PGF_{1\alpha}$ were batch analysed by a radioimmunoassay (Amersham International). The results were expressed as pg/ml.

TREATMENT ALLOCATION

All patients who had successful angioplasty received active PGI_2 or placebo buffer infusion according to their randomisation group for 36 hours after the procedure. The infusion syringes were changed by the pharmacy department every 10 hours because after this time PGI_2 activity lessens. Unless contraindicated all patients also received a nitrate infusion (2 mg/h Isoket) and heparin (1000 U/h), both for 24 h, as was unit policy at that time. Any symptoms during this time were recorded, particularly bradycardia, hypotension, flushing, or nausea. Patients were discharged on aspirin, the dose being determined according to the physicians' usual choice. Other drugs given on discharge were nitrate and/or calcium antagonist, again as chosen by the physician.

FOLLOW UP EVALUATION

Patients were routinely admitted six months after angioplasty and performed an exercise stress test (modified Bruce protocol). A full history was taken to highlight any symptoms during the previous six months as well as the current cardiac status. Angiography was

repeated in views identical with those used at the previous angioplasty.

Patients who were admitted *within* the six month follow up and who gave a history of angina that was thought by their physician to justify angiography were considered to have reached an end point of the study. For ethical reasons none of the patients who did not have angiographic restenosis within the six month follow up period had further angiography at six months.

QUANTITATIVE ANGIOGRAPHY

All angiograms obtained at routine six month follow up and those taken during early admission within the six months were analysed by quantitative videodensitometry. This was done without knowledge of the patient's randomisation group. The Vangard XR70 system was used to generate absolute diameters for both normal artery reference segments and for regions of maximal stenosis. Percentage stenotic narrowing was also calculated. Where possible orthogonal views were used, although this was not regarded as essential when the artery was foreshortened in the orthogonal view or where there was overlap, as was frequently the case with mid or distal light coronary artery lesions. The normal artery reference segment was taken to be as close as possible to the stenotic region but outside any area of normal artery involved in balloon inflation. To allow for vessel tapering, the diameter of the normal artery segment both proximal and distal to the stenosis was measured and the mean calculated. All measurements were recorded during a diastolic frame with the coronary arteries maximally filled. All measurements (normal proximal, normal distal, region of maximum severity) were taken three times and a mean value calculated. Results were obtained for stenotic lesions and normal arteries before and after angioplasty and from the follow up angiogram, whether at planned six month admission or from an earlier angiogram. The Vangard XR70 system has been extensively assessed against phantoms and postmortem coronary arteries[19 20] as well as against other quantitative systems such as the CAAS system[21] and has been shown to provide an accurate measurement of absolute diameter.

DATA ANALYSIS

The data were analysed as follows:

- Comparison of restenosis rates between PGI_2 and control groups.
- Comparison of absolute mean follow up luminal diameter (mm) in PGI_2 treated patients compared with control value.
- Comparison of absolute and relative gain and absolute and relative loss in PGI_2 and control groups.

RESTENOSIS DEFINITION

The restenosis rates in the two groups were determined according to the NHLBI IV definition which is based on a comparison between the stenotic region and a normal reference segment (restenosis being defined by loss of a 50% percentage gain). This definition has been shown to correlate with other relative definitions such as >50% at follow up.[22]

Relative definitions have their detractors, and we, like others, have used other means of comparing the effect of treatment on angiographic outcome after angioplasty. For example, we plotted the absolute diameter against the cumulative incidence for the treated and placebo group before, immediately after angioplasty, and at follow up.[23]

Recent evidence has indicated that restenosis is a continuous variable.[24] Therefore mean absolute diameter at follow up in the placebo group was quantitatively compared with absolute mean diameter for PGI_2 group, ensuring that we took account of any differences between groups in absolute diameters PTCA before and after. Relative loss and relative gain were thus calculated for the two groups.

STATISTICAL METHODS

Sample size

Sample size is dependent on the expected outcome required for the agent being tested. When this trial was set up, PGI_2 was known to be a powerful antiplatelet agent. None the less we thought its routine use was unlikely because of known powerful side effects unless it could be shown to have a significant impact on restenosis (that is, a 50% reduction in restenosis rates or in the loss of minimal luminal diameter). The mean restenosis rate calculated from the control population of 23 other trials was 36%. Power calculations at the onset of this study thus indicated that if we were to achieve our aim (to reduce the restenosis rate to about 18%) 73 patients would be required in each group to detect this difference. (85% power, $2p = 0{\cdot}05$).

To assess further the *effect of treatment* (rather than to compare restenosis rates), we have considered that the mean absolute difference in placebo group luminal diameter from immediately after PTCA to follow up was likely to be about 0·7 mm[24] with an approximate standard deviation of about 0·5 mm. To show a reduction to 0·35 mm in the difference produced by treatment would also require 73 patients/group.

Trial commencement

Because this was a study of the effect of a treatment on subsequent recurrence after successful angioplasty, the trial was deemed to have started when the patient had completed the 36 h infusion after successful angioplasty.

Comparison of quantitative angiographic data

Absolute diameters between and within the groups were compared by a non-parametric test (Mann Whitney U).

Platelet function tests

We used paired *t* tests to compare the platelet activation index in the samples taken before

and after angioplasty from the coronary sinus with those taken from the aorta.

End points

The end points for this trial were (*a*) cardiac death, (*b*) a history of angina sufficient to warrant admission leading to cardiac catheterisation, (*c*) admission with angina and electrocardiographic evidence of ischaemia if intervention (PTCA or coronary surgery) was undertaken without prior cardiac catheterisation, and (*d*) six month follow up angiogram.

Presentation of results

The results are presented as number (%) in each group defined as having restenosis (see above), as mean absolute values at follow up, and as acute relative gain versus late relative loss. Since the treatment being tested was a systemic treatment and might thus be expected to benefit all dilated lesions, the groups were analysed initially as patients rather than as lesions and a patient was considered to have restenosed when at least one lesion had restenosed.

Results

A total of 155 patients were randomised: 76 to PGI_2 (in buffer 4 ng/kg/h for 36 h) and 79 to placebo (buffer alone for 36 h). Angioplasty was unsuccessful because of failure to cross the lesion with a wire or balloon in seven of those initially randomised to active treatment and eight in controls. Of the 69 patients in PGI_2 group who went back to the ward with an infusion running, two suffered chest pain and ECG changes sufficient to warrant recatheterisation within the first 36 h (one at 0·5 h and one at 2 h: both had repeat angioplasty). Of the 71 patients in the placebo group, three required recatheterisation for chest pain and ECG symptoms within 36 h (one at 1 h, one at 75 min, and one at 5 h: all had repeat angioplasty. No acute deaths occurred. This left 67 patients in the prostacyclin arm of the study and 68 patients in the placebo arm.

SIDE EFFECTS DURING THE INFUSION PERIOD

Table 1 shows the incidence of reported side effects in the two groups during the infusion period. Flushing and headache are subjective effects. Hypotension was defined as a 20% reduction in previous systolic blood pressure and bradycardia as a heart rate <50 beats/min.

Table 1 Symptoms during the first 24 hours after the start of infusion.

Symptom	PGI_2 (n = 67)	Placebo (n = 68)
Flushing	8	4
Headache	9	6
Nausea	2	0
Vomiting	4	1
Hypotension*	3	1
Bradycardia†	3	1
Nodal rhythm	3	2
Intravenous nitrate	63	65

*Fall of ≤20% of initial measurement.
**Heart rate ≤50 beats/min.
†≤50 beats/min.

Table 2 Age, sex, and symptomatic presentation in the PGI_2 and control groups

Variable	PGI_2 (n = 67)	Control (n = 68)
Mean age (SD) (yr)	56 (8)	53 (8)
M/F	55/12	60/8
Angina grade*:		
0	0	0
1	0	0
2	21	23
3	26	24
4	20	21
Angina syndrome†:		
S	39	37
US	22	23
PMI	6	8
Duration:		
≥3 mnth	25	26
<3 mnth	42	42
Mean (SD)	9·2 (13·5)	8·8 (12·7)

*Canadian Cardiovascular Society Classification.
†S, stable; US, unstable; PMI, postmyocardial infarction.

BASELINE COMPARISON BETWEEN GROUPS

One hundred and thirty five patients therefore had successful angioplasty and completed the 36 h intravenous infusion: 67 in the treatment group and 68 in the placebo group.

There were no significant differences between the groups in terms of baseline characteristics (tables 2 and 3). The two groups were similar for mean age; proportion of men; spectrum of angina grade; numbers of patients with stable, unstable, or post-infarct angina; duration of angina (mean 9·2 months PGI_2 group and 8·8 months placebo group); and number of patients in each group who were past or current smokers or who had a history of hypertension or diabetes. (table 3). Admission medication was not significantly different in the two groups, and 55 of 67 in the PGI_2 group and 60 of 68 in the placebo group received aspirin during the six month follow up period. The target vessels were similar in both groups. Table 4 shows

Table 3 Comparison of lesion and patient factors in the PGI_2 and control groups

Factor	PGI_2 (n = 67)	Control (n = 68)
Smokers:		
Never	36	14
Ex/current	40	44
Hypertension	10	7
Diabetes	2	1
Admission medication:		
BB	47	40
CA	42	43
N	49	44
AS	18	17
D	10	1
Aspirin during trial	55	60
Lesion angioplastied single vessel disease:		
LAD prox	6	10
LAD mid	27	22
Cx	9	9
RCA prox	2	8
RCA mid	9	4
RCA distal	2	2
Single angioplasty	55	55
Double angioplasty	12	13

BB, β-blockers; CA, calcium antagonist; N, oral nitrate; A, aspirin; D, dipyridamole.

Table 4 Outcome of exercise stress tests in the PGI_2 and control groups before admission

Exercise stress tests before trial	*PGI_2 (n = 67)*	*Control (n = 68)*
No. undertaken*	48	42
Mean stage achieved	3·5	3·3
Mean heart rate	115	111
Positive tests (>1 mm ST depression/angina)	41	35
Negative tests	7	7

*No stress tests were undertaken in patients with unstable angina.

the exercise test data before angioplasty in the two groups. The number of positive tests and exercise stage achieved on admission were similar in the two groups.

Fifty five patients in each group underwent single vessel angioplasty. A further 12 in the PGI_2 group and 13 in the placebo group had double vessel angioplasty.

PATIENT OUTCOME

Figure 1 shows patient progress during the six month trial. Three patients died during the follow up period, one from cardiac causes (myocardial infarction at home four days after PTCA) and two from non-cardiac causes (one carcinoma of the liver and one adenocarcinoma of the lung). All three were in the placebo group. Twenty-three patients were admitted because of angina during the six month follow up (15 PGI_2, eight placebo). Fifteen (10 PGI_2, five placebo) were shown on subsequent quantitative angiography to have restenosis according to the NHLBI definition (IV). Three of the 23 patients admitted early proceeded straight to coronary surgery with no further angiogram (two PGI_2, one placebo) and five (three PGI_2, two placebo) of the 23 were thought on qualitative assessment of the angiogram at the time to not have developed restenosis. This was confirmed in all five by subsequent measurement with quantitative angiography. (Since the end point was the development of angina sufficient to warrant re-admission and need for cardiac catheterisation these patients were excluded for ethical reasons from planned further catheterisation at six months). At six months a further four patients (all placebo group) refused the follow up angiogram.

RESTENOSIS

Ten patients treated with PGI_2 had restenosis and were readmitted early as were five who received placebo. There were 105 other patients who were routinely admitted at mean 6·1 month (range 5·3–6·8 months) and who had follow up angiograms. This represents an overall 93% angiographic follow up. Twenty seven of the 105 patients had restenosis of at least one lesion according to definition IV (nine PGI_2, 18 placebo). The overall patient restenosis rate (including early admission) for the PGI_2 group was thus 19/65 (29·2%) *v* 23/60 (38·3%) for the placebo group (difference not significant) (fig 1).

LESION RESTENOSIS

Of the twenty-three patients who were re-admitted early, two of eight in the placebo group had had double vessel angioplasty (one had no restenosis in either lesion by either definition and one had restenosis in both lesions according to both definitions for one lesion and by only the NHLBI definition IV for the other lesion—this patient underwent repeat PTCA to both lesions). Of the fifteen patients who had had active treatment and had been admitted early, only one had double

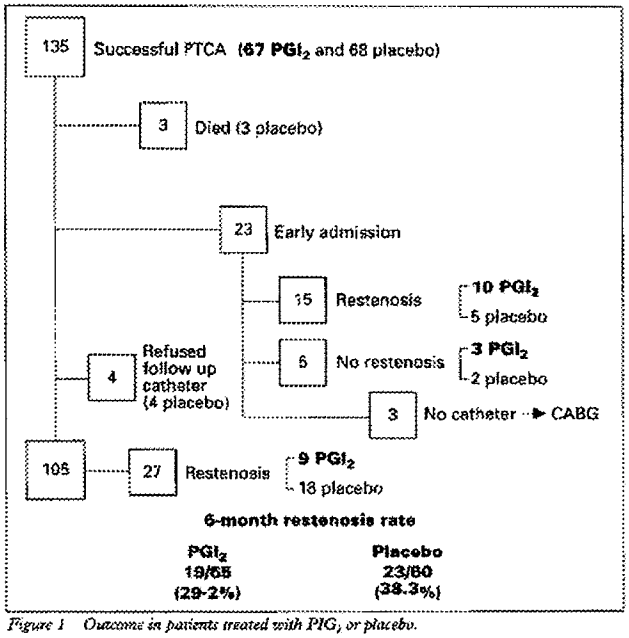

Figure 1 Outcome in patients treated with PGI_2 or placebo.

Table 5 Mean absolute diameters (SD) (mm) for normal reference and stenotic segments

	PGI_2	*Control*
Before angioplasty:		
Stenotic diameter	0·64(0·48)	0·63(0·52)
Normal diameter	3·29(0·62)	3·16(0·77)
After angioplasty:		
Stenotic diameter	2·48(0·57)*	2·21(0·59)
Normal diameter	3·14(0·68)	2·95(0·71)
Six month follow up:		
Stenotic diameter	1·83(0·88)	1·59(0·92)
Normal diameter	2·92(0·66)	2·75(0·60)

*p = 0·04

Table 6 Clinical outcome in the PGI_2 and control groups at six months

	PGI_2 (n = 52)	*Control (n = 53)*
Angina grade at six months:		
0	41	37
1	7	12
2	2	4
3	1	0
4	1	0
Exercise tests at 6 months:		
No. undertaken	51	53
Mean stage achieved	4·0	4·4
Mean heart rate	135	141
Positive tests (>1mm ST depression/angina)	8	6

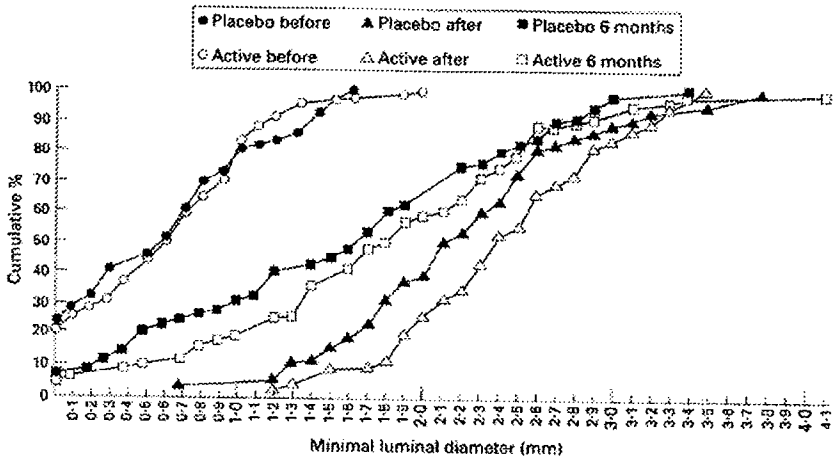

Figure 2 Cumulative percentage plotted against minimal luminal diameter for the PGI_2 and placebo groups before PTCA, after PTCA, and at 6 month follow up.

vessel disease this was diagnosed as restenosis of both lesions by both definitions.

The overall lesion restenosis rate was 22/79 (28%) for the PGI_2 group and 22/81 (27%) for control group.

ABSOLUTE MEASUREMENTS

Plotting the data for the cumulative incidence against the absolute diameter showed no obvious difference between the groups at follow up (fig 2). It is clear, however, that the mean post-stenotic diameter is different in the two groups (2·48 (0·57) mm *v* 2·21 (0·59) mm, p = 0·01). Thus the absolute gain was 1·84 (0·76) mm in the PGI_2 group and 1·58 (0·56) in the placebo group (p = 0·04). The relative gain (absolute gain/reference artery size) was also greater in the PGI_2 group 0·61 (0·20) *v* 0·56 (0·18) (NS). The absolute loss and relative loss in the PGI_2 group were however, also greater than in the placebo group although not significantly. Thus there was no significant difference between the actual minimal luminal diameters at follow up between the two groups (1·83 (0·88) mm *v* 1·59 (0·60) mm).

Table 5 shows the mean quantitative angiographic data for all lesions and fig 3 shows the absolute and relative acute gain and late loss.

CLINICAL OUTCOME

Table 6 shows the angina grade and exercise stress test results. At the six month follow up

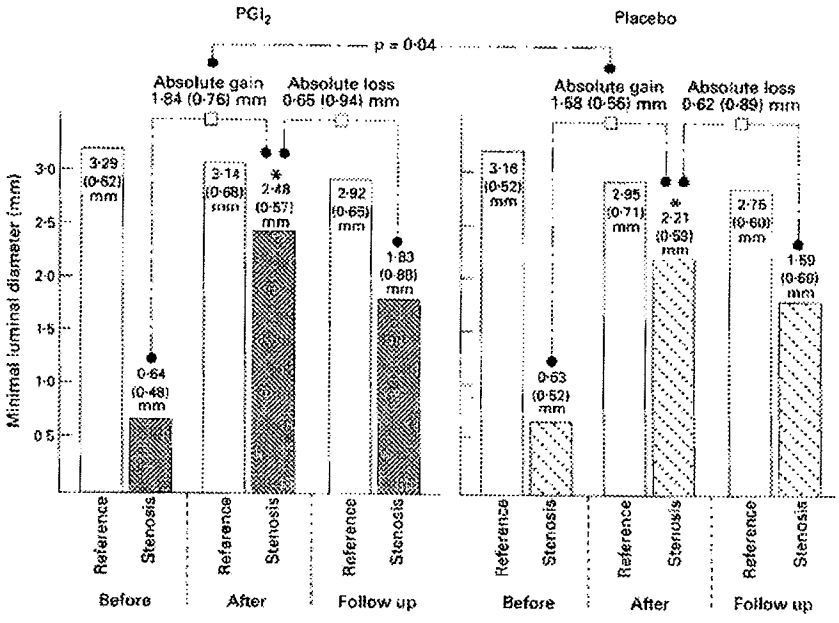

*Figure 3 Minimal luminal diameter in reference arteries (SD) and stenotic segments in the PGI_2 and placebo groups before PTCA, after PTCA, and at follow up. *p = 0·04 for absolute change post PTCA in PGI_2 group *v* absolute change post PTCA in placebo group.*

both groups showed a considerable improvement in both angina grade and exercise achieved (tables 2 and 4).

PLATELET DATA: AGGREGOMETRY

The 7F NIH catheter was the best one for sampling the coronary sinus from the leg. It was difficult to take samples from end hole catheters. A catheter was positioned correctly in only 24 patients in the PGI_2 group and 26 in the placebo group. In a further six patients in the PGI_2 group and three in the placebo group angioplasty took so long that the samples could not be transported to the haematology laboratory, be processed, and aggregometry performed within 2 h. These samples were discarded. Two of us (AHG and DSC) performed all the platelet function tests without knowledge of randomisation group.

In the placebo group the platelet activation index in samples taken from coronary sinus after angioplasty (CS2) was significantly higher than in samples from the aorta (A2) (11·2 (4·3) *v* 7·6 (2·8) p = 0·001: mean difference 3·8 (−5·89 to 1·86). The index was also higher than in coronary sinus samples taken before angioplasty. (CS2 *v* CS1 (7·4 (3·6)); p < 0·001 (mean difference = −4·02 (−5·91 to −2·06)). There was no significant difference between the indices in aortic samples taken before and after angioplasty (A1 7·6 (3·3 *v* A2 7·6 (2·8)).

The aggregometry results in the PGI_2 group were similar, with the mean platelet activation index (PAI) of 12·9 in coronary sinus samples taken after angioplasty. This value was significantly higher than the PAI of blood taken from the coronary sinus before angioplasty (CS1 8·8 (4·0), p < 0·001; mean difference −3·7 (−5·1 to −2·4)) and higher than that of aortic samples taken after angioplasty (A2 8·9 (3·0), p < 0·001; mean difference −3·60 (−5·17 to −2/04).

The concentration of 6-Keto-$PGF_{1\alpha}$ in blood taken from aortic and coronary sinus samples in the PGI_2 patients was significantly higher than that in the controls (mean 182·5 (66·2) pg/ml *v* < 2 pg/ml, p = < 0·001).

Discussion

Restenosis after angioplasty is thought to be the consequence of a complex interaction between blood factors, particularly platelets and the injured blood vessel wall. The complexity of the process may explain why so-called antiplatelet drugs such as aspirin[26] (which inhibits predominantly only one of the many intraplatelet metabolic pathways[27] do not affect restenosis. Other agents such as fish oils, steroids, angiotensin converting enzyme inhibitors, and antiplatelet-derived growth factor drugs such as trapidil[28] have also been tried in an attempt to reduce restenosis by pharmacological means. We considered that it was appropriate to investigate an agent that, in theory, affects intraplatelet pathways to a greater degree than aspirin and one that is reported to influence adhesion as well as aggregation, which aspirin does not. Epoprostenol (PGI_2), which has been shown to increase intraplatelet cAMP and to inhibit both aggregation and adhesion[29,30] in vitro and in animal models, seemed to be a reasonable candidate. The fact that normally it is concentrated in endothelial cells, a layer consistently shown to be removed during angioplasty, also made it theoretically attractive.

Epoprostenol (PGI_2) was thus started before angioplasty and given for 36 h thereafter. The time period was based on work of Mustard and his group, who showed that if platelets could be kept away from a damaged surface for 36 to 48 hours, smooth muscle cell proliferation might be reduced.[31] This fitted conveniently with the fact that when the trial started PGI_2 could only be given intravenously and patients were routinely discharged 48 hours after angioplasty.

The PGI_2 and placebo treated groups had similar baseline demographic features. The mean post-angioplasty minimal luminal diameter in the PGI_2 group was significantly higher than that in the placebo group. This should put the PGI_2 group at an advantage, just as the larger minimal diameter obtained with stents may advantage such patients.

The follow up rate for early symptom-related and late follow up angiography was high (93%) with quantitative analysis and assessment of restenosis based on two definitions that represented different philosophies. The trial was designed to evaluate the efficacy of PGI_2 in preventing restenosis after angioplasty. In an attempt to explain any pathophysiological effects we also measured platelet function.

ANALYSIS OF RESULTS

An intravenous infusion of PGI_2 given from before and for 36 h after angioplasty did not significantly reduce the incidence of restenosis as measured by six month quantitative angiography.

A plot of the absolute value against the cumulative incidence showed no obvious difference between the two groups at follow up. This method has become one way of presenting such trial data. Our data confirm the current concept of "the more you gain the more you lose" because there was no difference in the late minimal luminal diameters between the two groups. Our acute gain for both groups was higher than normally reported in other trials. This may reflect our undeclared policy at that time of only performing angioplasty to larger vessels (our mean reference diameters were 3 mm +) and/or our determination to achieve a satisfactory result.

REASONS FOR APPARENT FAILURE OF PGI_2 TO REDUCE RESTENOSIS OR IMPROVE ABSOLUTE LUMINAL VALUE AT FOLLOW UP

Study power

The power of the trial might have been too low to detect the difference in restenosis reduction that would now be thought achievable. None the less, there was a 24% reduction in restenosis rate. Most current

trials are evaluating drugs in the expectation of achieving an event reduction of 30% or less.[35] Detection of a 30% event reduction, be it binary (yes/no) restenosis rate or reduction in absolute late loss, requires a minimum of 230 patients per group and detection of an event reduction of 50% requires 73 patients per group. A lowered expectation (an arbitrary 30% rather than our 50%) was based on the difficulty in finding an agent that affects restenosis, which is a process that is proving to be extremely powerful biologically. At the start of this trial, however, a reduction from a mean restenosis rate of 36% (based on trial results available at that time) to 18% was deemed reasonable with the theoretically powerful agent we were testing. Whether in general one should aim for less of an effect (that is, a reduction of 30%) or try more powerful agents is a matter for debate. With an agent such as PGI_2 which may have significant side effects, it is clear that the potential benefit should outweigh the disadvantages. With powerful drugs one could argue for a target of a 50% event reduction, especially because 60–70% of patients do not restenose and would be receiving the agent for no good reason.

Though there was some initial patient dropout the numbers in each group would still have detected a 50% reduction in restenosis at 80% trial power. Our trial was set up to detect a 50% reduction and this may be the reason why a lesser benefit could not be demonstrated. However, other aspects of this study suggest that-PGI_2 in the doses infused did not significantly alter the basic biological process.

Platelet function tests

This is the first study that has attempted to show a change in platelet function as a consequence of treatment during PTCA. We used ex vivo platelet aggregometry as a test of the platelet/vessel wall interaction because it is cheap, reproducible, and has been shown to be affected by PGI_2 in other circumstances.[17] Aggregometry can be quantitated in several ways. We used a dose response curve to calculate the platelet activation index for a standardised platelet count. This has been validated in other models of the platelet vessel wall interaction[19] and is based on the concept that not all platelets that come into contact with a damaged vessel wall stick to it. Other tests of platelet function such as platelet factor 4, β thromboglobulin, and thromboxane A_2 generation have often been difficult to intepret because of the wide variance in normal valves between patients and between laboratories.[32] Others have assessed the effect of angioplasty on platelet function but in fewer patients.[33,34] A direct effect of angioplasty on ex vivo aggregometry has not been previously shown.

Our data clearly demonstrate that after angioplasty platelets in the coronary sinus are more sensitive to ex vivo aggregating agents. PGI_2 given in the trial dose did not however, inhibit the process. PGI_2 has both anti-aggregatory and antiadhesion properties: the antiadhesion properties are twenty times less powerful than the antiaggregating properties.[35] Because there was non demonstrable effect on aggregation it is unlikely that the intimate contact between adherent platelets and the damaged vessel was being inhibited. We believe that this adhesion is important in restenosis because it leads to the local release of platelet-derived growth factor. While it is possible that at the time of sampling there was not enough PGI_2 in the circulation, all patients had received at least 10 minutes of infusion before sampling and aggregometry was undertaken within 2 h.

In this study the presence of PGI_2 measured as 6-keto-$PGF_{1\alpha}$ in the coronary sinus of those patients given active treatment confirms our contention that PGI_2 was there, but in the dose given not powerful enough to limit platelet adherence. The dose used in this study was based on other studies in which it had been noted that frequent side effects occurred with doses of 5 ng/kg/hour or greater.[36] Even with a dose chosen to limit side effects, we found that the incidence of recognised side effects was higher in patients treated with PGI_2. It is likely that the vessel wall damage is such that drugs with a greater effect on adhesion (such as monocolonal antibodies against glycoprotein 1b) are required to counteract the adhesive properties of local type III collagen. Any agent designed to prevent such interactions should be present at the time of angioplasty and may need to be targeted locally to reduce the impact of powerful systemic side effects.[37]

Many agents have now been tested for their effect on restenosis. To date none, including aspirin at any dose, fish oils, steroids, thromboxane synthetase inhibitors, and thromboxane receptor blockers have consistently been shown to be of benefit. PGI_2 has been assessed in previous trials[26] over short infusion periods with initially similar results to this study. A recent review by Raizner *et al* has, however, revised these results.[38] This group confirmed that patients randomised to Ciprostene had better clinical outcome at six months than control group (clinical events 23% *v* 39%, $p = 0{\cdot}004$). Reanalysis of the data derived from quantitative angiography now suggests that the late loss may have been significantly less for the ciprostene group (0·32 (0·07) *v* 0·57 (0·08) mm, $p = 0{\cdot}025$). These data support the contention that PGI_2 given during angioplasty may be having some effect, although Raizner *et al* were only able to retrieve 83% of treated and 88% of control angiograms. Our data indicate that this group's contention that "Ciprostene warrants consideration was adjunctive treatment for the prevention of restenosis in PTCA" is not yet confirmed.

The only "antiplatelet" approach that has been successful so far reducing intimal hyperplasia has been to make animals severely thrombocytopenic.[39] If such a significant degree of platelet change is required then limiting restenosis will prove difficult.

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Journal of the American College of Cardiology/*Contents in brief*

JULY 1998 VOLUME 32 NUMBER 1

Journal of the American College of Cardiology (ISSN 0735-1097) is issued monthly, except semimonthly in March and November, in two indexed volumes per year by Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA at 500 Cadmus Lane, Easton, MD 21601-3969. Subscription prices per year: For customers in the USA only: institutional rate: US$ 236.00, personal rate: US$ 152.00, student/resident rate: US$ 92.00. For surface mail delivery to customers in Europe, The CIS, and Japan: institutional rate: NLG 583.00, personal rate: NLG 437.00, student/resident rate: NLG 332.00. For surface mail delivery to customers in all other countries: institutional rate: US$ 335.00, personal rate: US$ 251.00, student/resident rate: US$ 191.00. For surface airlift delivery to customers in Europe: institutional rate: NLG 783.00, personal rate: NLG 637.00, student/resident rate: NLG 532.00. For surface airlift to customers in Japan: institutional rate: NLG 896.00, personal rate: NLG 750.00, student/resident rate: NLG 646.00. Prices include postage and are subject to change without notice. Periodicals postage paid at New York, NY and at additional mailing offices. Postmaster: Send address changes to *Journal of the American College of Cardiology*, Elsevier Science Inc., 655 Avenue of the Americas, New York, NY 10010.

0735-1097(199807)32:1;1-S